[redacted]

STATISTICAL ANALYSIS PLAN

A Phase 2, Randomized, Multicenter, Masked, Parallel-Group, Dose Response Study Evaluating the Safety and Efficacy of NCX 470 (3 doses: 0.021%, 0.042%, and 0.065%) vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension

Sponsor: Nicox Ophthalmics, Inc.

Protocol Number: NCX-470-17001

Author: [redacted]

Date: September 23, 2019

Version: Final 2.0

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[redacted]

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Statistical Analysis Plan Approval

[redacted]

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List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CSR	Clinical Study Report
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
[redacted]	[redacted]
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
QD	Once Daily
RTF	Rich Text Format
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol Version 2.0 dated 23-OCT-2018.

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

The primary objective is to demonstrate that the mean diurnal intraocular pressure (IOP) reduction at the Week 4 Visit with NCX 470 once daily (QD) is non-inferior to latanoprost 0.005% QD for one of the tested concentrations of NCX 470.

A secondary objective is to demonstrate that the mean diurnal IOP reduction at the Week 4 Visit with NCX 470 QD is superior to latanoprost 0.005% QD for one of the tested concentrations of NCX 470.

Another secondary objective is to demonstrate that one of the tested concentrations of NCX 470 is safe and well tolerated.

2.1 Study Endpoints

2.1.1 Efficacy Endpoints

The primary efficacy endpoint is the reduction from baseline (based on Eligibility 1 and Eligibility 2 Visits) in mean diurnal IOP at the Week 4 Visit in the study eye.

- Secondary Endpoints:
  - Reductions from baseline in time-matched IOP measured at 8 AM, 10 AM, and 4 PM at the Week 4 Visit for the study eye.
  - Reductions from baseline in mean diurnal IOP measured at the Week 1 Visit, Week 2 Visit, and at the Exit Visit for the study eye.
  - [redacted]

2.1.2 Safety Endpoints

Safety assessments will include

- Rate of discontinuation from study
- Adverse events (AEs)

as well as changes in the following:

- IOP
- Slit-lamp biomicroscopy
- Conjunctival hyperemia
- Dilated ophthalmoscopy
- Pachymetry
- Best-corrected visual acuity (BCVA)
- Vital signs
- Non-fasting clinical laboratory tests
- Urine pregnancy tests for females of child-bearing potential

2.2 Primary Hypotheses

The primary hypotheses are:

- Testing NCX 470 ophthalmic solution, 0.021% non-inferior to latanoprost ophthalmic solution, 0.005%.

  H_0: The difference between study eyes treated with NCX 470 0.021% and latanoprost 0.005% (NCX 470 – latanoprost) in the mean diurnal IOP change from baseline at the Week 4 Visit, is ≥ 1.5 mmHg.

  H_a: The difference between study eyes treated with NCX 470 0.021% and latanoprost 0.005% (NCX 470 – latanoprost) in the mean diurnal IOP change from baseline at the Week 4 Visit, is < 1.5 mmHg.

  NCX 470 0.021% will be non-inferior to latanoprost if the null hypothesis (H_0) is rejected (i.e., the upper limit of the two-sided 95% CI around the differences between the LS mean of NCX 470 0.021% and the LS mean of the latanoprost group [NCX 470 – latanoprost] is < 1.5 mmHg). If NCX 470 0.021% is non-inferior to latanoprost, then the superiority of the NCX470 0.021% to latanoprost will be tested. NCX 470 0.021% will be superior to latanoprost if the p-value for the testing treatment difference is <= 0.05 and the LS mean difference in change from baseline at Week 4 visit (NCX470 – latanoprost) is < 0.

- Testing NCX 470 ophthalmic solution, 0.042% non-inferior to latanoprost ophthalmic solution, 0.005%.

  H_0: The difference between study eyes treated with NCX 470 0.042% and latanoprost 0.005% (NCX 470 – latanoprost) in the mean diurnal IOP change from baseline at the Week 4 Visit, is ≥ 1.5 mmHg.

H_a: The difference between study eyes treated with NCX 470 0.042% and latanoprost 0.005% (NCX 470 – latanoprost) in the mean diurnal IOP change from baseline at the Week 4 Visit is <1.5 mmHg.

NCX 470 0.042% will be non-inferior to latanoprost if the null hypothesis (H_0) is rejected (i.e., the upper limit of the two-sided 95% CI around the differences between the LS mean of NCX 470 0.042% and the LS mean of the latanoprost group [NCX 470 – latanoprost] is < 1.5 mmHg). If NCX 470 0.042% is non-inferior to latanoprost, then the superiority of the NCX470 0.042% to latanoprost will be tested. NCX 470 0.042% will be superior to latanoprost if the p-value for the testing treatment difference is <= 0.05 and the LS mean difference in change from baseline at Week 4 visit (NCX470 – latanoprost) is < 0.

- Testing NCX 470 ophthalmic solution, 0.065% non-inferior to latanoprost ophthalmic solution, 0.005%.

H_0: The difference between study eyes treated with NCX 470 0.065% and latanoprost 0.005% (NCX 470 – latanoprost), in the mean diurnal IOP change from baseline at the Week 4 Visit, is ≥ 1.5 mmHg.

H_a: The difference between study eyes treated with NCX 470 0.065% and latanoprost 0.005% (NCX 470 – latanoprost), in the mean diurnal IOP change from baseline at the Week 4 Visit, is < 1.5 mmHg.

NCX 470 0.065% will be non-inferior to latanoprost if the null hypothesis (H_0) is rejected (i.e., the upper limit of the two-sided 95% CI around the differences between the LS mean of NCX 470 0.065% and the LS mean of the latanoprost group [NCX 470 – latanoprost] is < 1.5 mmHg). If NCX 470 0.065% is non-inferior to latanoprost, then the superiority of the NCX470 0.065% to latanoprost will be tested. NCX 470 0.065% will be superior to latanoprost if the p-value for the testing treatment difference is <= 0.05 and the LS mean difference in change from baseline at Week 4 visit (NCX470 – latanoprost) is < 0.

Multiple comparison adjustment will not be applied given that it is a Phase 2 study.

3. Study Design and Procedures

3.1 General Study Design

This is a randomized, multicenter, masked, parallel-group, dose-response phase 2 clinical study. This study will be conducted in approximately 20 sites in the United States. Up to 10 will be added based on enrollment rates. Approximately 550 subjects will be screened and 420 will be randomized.

[redacted]

Subjects will be assessed for initial eligibility at the Screening Visit (Figure 1). Subjects currently being treated with an IOP-lowering medication (pretreated) will be required to discontinue their IOP-lowering medication during a washout period which will occur between the Screening Visit and the Eligibility 1 Visit. The length of the washout period will be determined based on the type of IOP-lowering medication used by the subject. Treatment-naïve subjects' Eligibility 1 Visit will be scheduled a minimum of 5 days after the Screening Visit to allow review of clinical laboratory results.

Successful washout and IOP-based eligibility for all subjects will be determined at the Eligibility 1 Visit (Day -7 to -3) and the Eligibility 2 Visit (Day 1) with diurnal IOP measurements at 8 AM, 10 AM, and 4 PM at both visits. The baseline IOP for all study analyses will be based on the study eye mean diurnal IOP from the Eligibility 1 and Eligibility 2 Visits. Subjects meeting eligibility requirements will be randomized. Study medication will be dispensed at the end of the Eligibility 2 Visit.

Subjects will be randomized in a 1:1:1:1 ratio to receive NCX 470 or latanoprost one drop in both eyes, QD in the evening:

- NCX 470 ophthalmic solution, 0.021%
- NCX 470 ophthalmic solution, 0.042%
- NCX 470 ophthalmic solution, 0.065%
- Latanoprost ophthalmic solution, 0.005%

Both eyes will be treated for the duration of the study. The study eye will be the eye with the highest baseline IOP value or the right eye if both eyes of a subject have the same IOP value at baseline. The contralateral eye will be considered as the fellow eye.

All doses will be self-administered or administered by a caregiver topically as eye drops in the evening.

A subject will be considered as having completed the study after completion of the Exit Visit.

3.2 Schedule of Visits and Assessments

Schedule of clinical assessments/procedures is presented in Appendix 1.

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

At the Eligibility 2 Visit (Day 1), utilizing the Interactive Response Technology (IRT) system, approximately 420 eligible subjects will be randomly assigned to one of three concentrations of NCX 470 or the active comparator latanoprost 0.005% solution in a masked fashion in a 1:1:1:1 ratio, based on a randomization schedule prepared by an independent biostatistician, who was not involved in the day-to-day conduct of the study. [redacted]

4.2 Masking and Unmasking

Treatment assignments will be masked to the Investigators, site staff involved in the clinical study, the Sponsor team members involved in the day-to-day oversight of the clinical study, the Medical Monitor, the employees of [redacted] administrating the study for the Sponsor, and the study subjects. The unmasked site designee will not perform any other study activities except handling study medication.

If unmasking of a subject becomes critical to the subject's safety, the Principal Investigator must authorize such decision. If possible, such decision should be first consulted with both the study Sponsor and the Medical Monitor. The study treatment assignment of a subject should be unmasked via the IRT. In a situation when the IRT system is not accessible, the unmasking can be achieved via scratch-off portion of the study kit label located in the source documentation. The Sponsor and the Medical Monitor must be notified within 24-hours following an emergency unmasking of any subject.

5. Sample Size and Power Considerations

[redacted]

[redacted]

6. Analysis Populations

Three different populations will be used in the analysis: an intent-to-treat (ITT) population, a per protocol (PP) population, and a safety population.

The ITT population will include all randomized subjects. Demographics, baseline characteristics, and efficacy variables will be analyzed using the ITT population. These analyses will be performed on an as-randomized basis.

The PP population will include all randomized subjects who received study medication, who had at least one follow-up visit and who had no major protocol deviations during the 28-day treatment period. The major protocol deviations will be determined and approved by Nicox prior to database lock. Demographics, baseline characteristics, and selected efficacy variables (refer to Table 11-1) will be analyzed using the PP population, in addition to the ITT population. These analyses will be performed on an as-treated basis.

The safety population will include all randomized subjects who received at least one dose of the study medication during the 28-day treatment period and will be used for the safety analyses. All safety variables will be analyzed on an as-treated basis using the safety population.

7. General Statistical Considerations

7.1 Unit of Analysis

The unit of analysis in this study will be the study eyes for all efficacy analysis unless specified otherwise. The safety summaries will be performed for study eyes and fellow eyes separately, as applicable. Disposition, demographics, baseline characteristics, medical history, concomitant medications, study drug exposure and AEs will be summarized at subject level.

7.2 Missing Data Handling

The primary efficacy analysis will be based on observed data, without imputation of missing data. [redacted]

Missing data will be not imputed for other efficacy analyses and safety summaries.

7.3 IOP Values for Analysis

Each subject's IOP will be measured at the Screening Visit and at the 8 AM, 10 AM, and 4 PM time points at the Eligibility 1, Eligibility 2, Week 1, Week 2, Week 4, and Exit Visits.

There will be 2 or 3 readings of IOP in each eye for each time point at each visit. For each eye, the mean will be used if there are 2 readings, or the median will be used if there are

3 readings of IOP. The means or the medians (i.e. the time-matched IOP values) will be the 'base' values for the calculation of mean diurnal IOP values and IOP analyses.

Mean diurnal IOP value for a specific visit will be calculated as an average of IOP values from the three timepoints (8 AM, 10 AM, and 4 PM) for the specific visit.

Baseline mean diurnal IOP will be calculated as an average of the mean diurnal IOP values at the Eligibility 1 and Eligibility 2 Visits.

Time-matched baseline IOP will be calculated as an average of the IOP values at the 8 AM time point from the Eligibility 1 and Eligibility 2 visits for the 8 AM time point of each post-baseline visit; an average of the IOP values at the 10 AM time point from the Eligibility 1 and Eligibility 2 visits for the 10 AM time points of each post-baseline visit; and an average of the IOP values at the 4 PM time point from the Eligibility 1 and Eligibility 2 visits for the 4 PM time point of each post-baseline visit.

7.4 Baseline Definition for Variables Other Than IOP

Baseline is defined as the last measurement prior to the first administration of study drug. Change from baseline will be calculated as follow-up visit minus baseline visit.

7.5 Data Analysis Conventions

All data analysis will be performed [redacted] after the study is completed and the database has been locked. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Outputs 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 (as applicable) based on all randomized subjects unless otherwise specified. Additional data listings will be provided as described in the sections for the data analyses.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), standard error (SE), 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. SDs 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. 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."

For efficacy analyses, unscheduled visits and early termination visits will be mapped to scheduled visits if they fall into the scheduled visit windows. If there are more than

1 assessment that fall into a scheduled visit window afer the mapping, the assessment at original scheduled visit will be used.

For safety analyses, Unscheduled Visits will be excluded from analyses and early termination visits will be combined with Exit Visits for analyses.

8. Disposition of Subjects

Analysis populations, study completion, discontinuation from the study, reasons for discontinuation from the study, subjects with any protocol deviations, subjects with major deviations, and subjects with minor deviations will be summarized for all randomized subjects using number of subjects and percentages. Reasons of withdrawal include: AE, lost to follow-up, Investigator decision, Sponsor or Institutional Review Board (IRB) decision, protocol violation, study termination by Sponsor, withdrawal by subject, IOP greater than 36 mmHg, and other.

9. Demographics and Baseline Characteristics

The demographic variables collected in this study include age, age category (>=18 to < 65, >=65, >= 75 years), sex, race, ethnicity and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for the ITT population and the PP population, separately.

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.

The following baseline variables for study eyes will be summarized for the ITT and PP population, separately:

- Baseline mean diurnal IOP
- Central corneal thickness
- Cup to disc ratio (horizontal)
- Cup to disc ratio (vertical)
- BCVA
- Conjunctival hyperemia [redacted]

Visual field and gonioscopy assessments will be performed at Screening Visit. The results will be presented in subject data listings.

10. Medical History and Concomitant Medications

10.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0.

Ocular medical history and non-ocular medical history will be summarized at the subject level based on the safety population, separately. If a subject reports the same preferred term (PT) multiple times within the same system organ class (SOC), the subject will only be counted once for the SOC. As with the PT, if a subject reports multiple conditions within the same PT, that subject will only be counted once for the PT.

10.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (Global B3, March 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 (e.g., 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."

Prior and concomitant medications will be summarized separately at subject level using the safety population. Medications will be tabulated for each treatment group using number of subjects 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. Prior medications will be defined as mediations used prior to the first dose of study drug. Concomitant medications will be defined as medications used on/after the first dose of study drug.

11. Efficacy Analyses

All primary and secondary efficacy variables, along with the planned analysis methods for those variables, are given in Table 11-1. These analyses will be performed for the ITT population for all efficacy variables and PP population for selected efficacy variables. The ITT population will be used for all efficacy subgroup analyses. Note that each subject will have one eye designated as the study eye. Only study eyes will be evaluated for all of the efficacy measures, except that, fellow eyes will also be evaluated separately for the analysis of the primary efficacy endpoint.

All efficacy variables will be summarized by treatment descriptively.

Table 11-1 Summary of Efficacy Variables and Analysis Methods

Efficacy Variable	T-test[1]	ANCOVA or ANOVA[2]	[redacted]	Analysis Population	Missing Data Imputation
Primary Analysis					
Mean change from baseline in mean diurnal IOP at the Week 4 Visit for study eyes	X	X		ITT	Observed data
[redacted]					
[redacted]					
Secondary Analysis					
Change from baseline in mean diurnal IOP measured at the Week 1, Week 2, and Exit Visits for the study eyes	X	X		ITT, [redacted]	Observed data

[redacted]

Efficacy Variable	T-test[1]	ANCOVA or ANOVA[2]	[redacted]	Analysis Population	Missing Data Imputation
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

[redacted]

Efficacy Variable	T-test[1]	ANCOVA or ANOVA[2]	[redacted]	Analysis Population	Missing Data Imputation
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

[redacted]

Efficacy Variable	T-test[1]	ANCOVA or ANOVA[2]	[redacted]	Analysis Population	Missing Data Imputation
[redacted]					

[2]Analysis of covariance (ANCOVA) model includes treatment as the main effect and baseline as the covariate. Individual models will be fit for each visit and time point as applicable. Analysis of variance (ANOVA) model includes treatment as the main effect. Individual models will be fit for each visit and time point as applicable.

[redacted]

11.1 Primary Analysis

The primary efficacy variable is the change from baseline in mean diurnal IOP to Week 4 visit, calculated as mean diurnal IOP at Week 4 visit minus baseline mean diurnal IOP. Baseline is based on Eligibility 1 and Eligibility 2 Visits measurements (See Section 7.3).

The primary efficacy assessment is the non-inferiority analysis of the difference in the treatment effect between each NCX 470 dose and latanoprost 0.005% in change from baseline in mean diurnal IOP to the Week 4 Visit, based on study eyes for the ITT population using observed data.

An analysis of covariance (ANCOVA) model with fixed-effect terms for baseline mean diurnal IOP, treatment, and treatment-by-baseline interaction will be performed. The treatment-by- baseline interaction term will be used to check the appropriateness of the ANCOVA model for testing parallelism among the slopes by treatment group. If the test of parallelism is not significant ($p \geq 0.10$), then the treatment-by-baseline interaction term will be dropped from the model and a reduced ANCOVA model with fixed-effect terms for baseline and treatment will be fit. If the test of parallelism is significant

($p < 0.10$), then an analysis of variance (ANOVA) model with fixed-effect term for treatment will be performed instead.

The LS mean of each of the NCX 470 treatment groups and latanoprost will be obtained from the ANCOVA or ANOVA. Each of the NCX 470 treatment groups will be compared with the latanoprost group by computing a two-sided 95% CI around the differences between the LS mean of each of the NCX 470 treatment groups and the LS mean of the latanoprost group. The differences between treatment groups will be calculated as each NCX 470 dose and all NCX 470 minus latanoprost correspondingly. For each comparison, the two-sided p-values will also be presented. Similarly, pairwise differences between NCX 470 doses will also be compared in the same way for informational purposes.

[redacted]

[redacted]

11.3 Secondary Analyses

Secondary efficacy variables include:

1. Mean diurnal IOP measured at the Week 1, Week 2, Week 4 and Exit Visits for the study eyes, using observed data, [redacted]

[redacted]

4. [redacted]

[redacted]

7. [redacted]

[redacted]

[redacted]

12. Safety Analyses

All safety summaries will be based on the safety population.

12.1 Exposure Duration of Study Drug and Compliance

Descriptive summary statistics by treatment will be presented for treatment exposure duration and compliance. Treatment exposure duration will be defined as the number of days that the subject was exposed to study treatment as calculated using the formula:

Exposure Duration = Date of last dose – Date of first dose + 1.

Compliance of study drug is calculated as:

100 * (number of days with study drug taken) / (exposure duration in days)

In addition, compliance will also be summarized by treatment using the number and percentage of subjects in category of < 90%, 90 – 110 %, and > 110%.

12.2 Adverse Events

AEs will be coded using MedDRA, Version 21.0.

Treatment-emergent AEs (TEAEs) include all AEs occurring after the first dose of study drug.

An overall summary by treatment group will be presented that includes the number and percentage of subjects who experienced at least one ocular TEAE, ocular serious TEAE, ocular TEAEs by strongest relationship to study drug, ocular TEAEs by maximum severity, ocular TEAEs leading to study drug withdrawal, the number and percentage of subjects who experienced at least one non-ocular TEAE, non-ocular serious TEAE, non-ocular TEAEs by strongest relationship to study drug, non-ocular TEAEs by maximum severity, non-ocular TEAEs leading to study drug withdrawal, and death.

The number and percentages of subjects with the TEAEs listed below will be summarized by SOC, PT, and treatment separately. If a subject reports the same PT multiple times within the same SOC, that subject will only be counted once for the SOC. As with the PT, if a subject reports multiple conditions within the same PT, that subject will only be counted once for the PT.

- Ocular TEAEs
- Non-ocular TEAEs
- Ocular serious TEAEs
- Non-ocular serious TEAEs
- Ocular TEAEs by maximal severity
- Ocular TEAEs by strongest relationship to study drug

- Ocular TEAEs leading to study drug withdrawal
- Non-ocular TEAEs by maximal severity
- Non-ocular TEAEs by strongest relationship to study drug
- Non-ocular TEAEs leading to study drug withdrawal

All TEAEs, TEAEs leading to study drug withdrawal, and all serious TEAEs will be presented in subject data listings.

12.3 Best-Corrected Visual Acuity (Early Treatment of Diabetic Retinopathy Study [ETDRS])

Best-Corrected Visual Acuity (BCVA) will be assessed at the Screening, Eligibility 1, Eligibility 2, Week 1, Week 2, Week 4, and Exit Visits. The logarithm of the minimum angle of resolution (logMAR) BCVA will be summarized by treatment at each visit using continuous summaries, including change from baseline, for both the study eyes and the fellow eyes. [redacted]

12.4 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination will be performed for eyelid, conjunctiva, cornea, lens, iris/pupil, and anterior chamber in both eyes at the Screening, Eligibility 1, Eligibility 2, Week 1, Week 2, Week 4, and Exit Visits.

The results (normal, abnormal [not clinically significant], abnormal [clinically significant]) for each parameter at each visit will be summarized by treatment using number of subjects and percentages in each result category, for the study eyes and the fellow eyes separately. Percentages will be based on the number of specific eyes with non-missing assessments at the given visit. [redacted]

12.5 Conjunctival Hyperemia

Conjunctival hyperemia will be assessed in both eyes at the Screening, Eligibility 1, Eligibility 2, Week 1, Week 2, Week 4, and Exit Visits.

[redacted]

12.6 Dilated Ophthalmoscopy Examination

A dilated ophthalmoscopy examination of the vitreous, retina, macula, choroid, and optic nerve will be performed in both eyes at the Screening and Exit Visits. The results (normal, abnormal [not clinically significant], abnormal [clinically significant]) for each parameter at

each visit will be summarized by treatment using number of subjects and percentages in each result category, for study eyes and fellow eyes separately. Percentages will be based on the number of specific eyes with non-missing assessments at the given visit. A shift table will also be provided comparing the Exit Visit to Screening Visit.

In addition, cup to disc ratios (horizontal and vertical) will be assessed in both eyes at the Screening and Exit Visits. The results will be summarized by treatment at each visit using continuous summaries, including change from screening, for the study eyes and the fellow eyes separately.

12.7 Anterior Chamber

Anterior chamber will be assessed in both eyes at the Screening, Eligibility 1, Eligibility 2, Week 1, Week 2, Week 4, and Exit Visits. The results below will be summarized by treatment at each visit by number of subjects and percentages in each result category, for the study eyes and the fellow eyes separately. Percentages will be based on the number of specific eyes with non-missing assessments at the given visit.

- [redacted]

[redacted].

12.8 Pachymetry

Pachymetry assessment will be performed at the Screening, Eligibility 2, and Week 4 Visits for both eyes. There will be 3 readings of central corneal thickness in each eye at each visit. The average (rounded to integer) of 3 readings will be used as central corneal thickness value for summaries.

The central corneal thickness values will be summarized by treatment at each visit using continuous summaries, including change from baseline, for the study eyes and the fellow eyes separately.

12.9 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) assessment will be performed at the Screening, Eligibility 1, Eligibility 2, Week 1, Week 2, Week 4 and Exit Visits. For each visit, two measurements for systolic blood pressure and diastolic

blood pressure will be obtained and the average will be reported. If the first two measurements differ by more than 5 mmHg (systolic or diastolic), then a third measurement will be obtained and the average will be reported. Rounding of the average value will be the nearest whole number. The average values will be summarized by treatment at each visit using continuous summaries, including change from baseline.

12.10 Clinical Laboratory Tests and Urine Pregnancy Test

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at Screening and Exit Visits.

For serum chemistry and hematology, the results for each parameter will be summarized by treatment at each visit using continuous summaries, including change from screening. Shift tables will also be provided comparing Exit Visit with Screening Visit.

For urinalysis, the categorical results for each parameter will be summarized by treatment at each visit using number of subjects and percentages for each result category. The numeric results for each parameter, if any, will be summarized by treatment at each visit using continuous summaries, including change from screening.

Urine pregnancy test results will be provided in a data listing.

[redacted]

13. Interim Analyses

No interim analysis is planned for this study.

14. Changes from Protocol-Stated Analyses

No changes from protocol-stated analyses.

15. Changes from Statistical Analysis Plan

Changes from this statistical analysis plan will be described in the statistical analysis section of the CSR.

16. 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)

17. Appendix Schedule of Clinical Assessments/Procedures

Event	Screening Visit	Eligibility 1 Visit Day -7 to -3			Eligibility 2 Visit Day 1			Week 1 Visit Day 7 [redacted]			Week 2 Visit Day 14 [redacted]			Week 4 Visit Day 28 [redacted]			Exit Visit[i] Day 29 [redacted]		
		8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM
Informed consent	X																		
Screening number (IRT/EDC)	X																		
Demographics	X																		
Medical/Ophthalmic history	X																		
Concomitant medications[a]	X		X			X			X			X			X			X	
[redacted]	[redacted]	[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]		
[redacted]	[redacted]																[redacted]		
[redacted]	[redacted]	[redacted]															[redacted]		
[redacted]	[redacted]																		
[redacted]	[redacted]	[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]		
[redacted]	[redacted]																		
[redacted]	[redacted]	[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]		
[redacted]	[redacted]	[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]		
[redacted]	[redacted]													[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]						[redacted]									[redacted]			
[redacted]	[redacted]																		
[redacted]	[redacted]																		[redacted]
[redacted]	[redacted]																		
Adverse events[f]	X		X			X			X			X			X			X	
Randomization (IRT/EDC)[g]							X												
Dispense study medication[h]							X												
Collect study medication														X					
Dispense/collect subject diary[i]							X		X			X			X				

[redacted]

Study exit (IRT/EDC)									X

[redacted]

[redacted]

18. List of Tables and Listings

18.1 List of Tables

Table number	Title	Population
[redacted]		

[redacted]

Table number	Title	Population
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Table number	Title	Population
[redacted]	[redacted]	[redacted]

[redacted]

Table number	Title	Population
[redacted]	[redacted]	[redacted]

[redacted]

Table number	Title	Population
[redacted]	[redacted]	[redacted]

[redacted]

18.2 List of Listings

Listing number	Title	Population
[redacted]		