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STATISTICAL ANALYSIS PLAN

A Multi-Center, Randomized, Double-Masked, Placebo-Controlled, Phase 2b Study Evaluating the Safety and Efficacy of NCX 4251 (Fluticasone Propionate Nanocrystal) Ophthalmic Suspension, 0.1% QD for the Treatment of Acute Exacerbations of Blepharitis (Mississippi)

Sponsor: Nicox Ophthalmics, Inc.

Protocol Number: NCX-4251-02

Author: [redacted]

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List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
[redacted]	[redacted]
Ecrf	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
[redacted]	[redacted]
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
logMAR	Logarithm of the Minimum Angle of Resolution
MAR	Missing at Random
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
[redacted]	[redacted]
[redacted]	[redacted]
OD	*Oculus Dextrus* (Right Eye)
[redacted]	[redacted]
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
QD	*Quaque Die* (Once Daily)
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SDTM	Study Data Tabulation Model
SEM	Standard Error of the Mean
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
[redacted]	[redacted]
VAS	Visual Analog Scale
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol NCX-4251-02, Version 4.0 dated 24 Mar 2021. This SAP describes the final analyses for complete data as no interim analyses are planned for this study.

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

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

2. Study Objectives

The objective of this clinical study is to evaluate the safety and efficacy of NCX 4251 Ophthalmic Suspension, 0.1% vs placebo for the treatment of the signs and symptoms of an acute exacerbation of blepharitis.

2.1 Primary Objective

The primary objective of this clinical study is to evaluate the proportion of subjects with complete cure (Score 0) in the composite (sum) score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at the Day 15 Visit for NCX 4251 treated subjects compared to placebo.

2.2 Secondary Objectives

The secondary objective of the study is to evaluate the mean change from baseline in Eye Dryness evaluated using the Visual Analog Scale (VAS) and Fluorescein Staining of inferior cornea at the Day 15 Visit for NCX 4251 compared to placebo.

3. Study Variables

The following will be collected during the course of the study:

- Signs and symptoms of blepharitis (Eyelid Debris, Eyelid Margin Redness, and Eyelid Discomfort)
- Eye Dryness symptoms using the VAS
- [redacted]
- [redacted]
- Corneal [redacted] staining (Fluorescein [redacted]
- [redacted]
- [redacted]

- Slit-lamp biomicroscopy
- Intraocular pressure (IOP)
- Dilated ophthalmoscopy
- Best-corrected visual acuity (BCVA)
- Urine pregnancy tests (for females of childbearing potential)
- Adverse Events (AE)
- Concomitant Medications

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

The primary endpoint for this study is:

- Proportion of subjects with Complete Cure (Score 0) in each of the following: Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at the Day 15 Visit.

3.1.2 Secondary Efficacy Endpoints

The secondary endpoints for this study are:

- Mean change from baseline in the Eye Dryness Symptoms using the VAS at the Day 15 Visit; and
- Mean change from baseline in Fluorescein Staining of the inferior cornea at the Day 15 Visit.

3.2 Safety Endpoints

The safety endpoints include the following:

- The incidence of treatment-emergent ocular and systemic AEs
- BCVA, IOP, ocular signs (as assessed by slit lamp biomicroscopy), and fundus assessments

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- [redacted]
- [redacted]
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- [redacted]
- [redacted]

3.4 Statistical Hypotheses

The primary objective of this study is to test whether the proportion of subjects with complete cure (Score 0) in the composite (sum) score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at the Day 15 Visit for NCX-4251-treated subjects is statistically superior to placebo-treated subjects using a two-sided alpha=0.05.

The two secondary endpoints will test if the mean reduction from baseline in Eye Dryness evaluated on the VAS and/or Fluorescein Staining of inferior cornea at the Day 15 Visit for NCX 4251 is statistically superior to placebo. The Hochberg correction for multiple testing will be performed to maintain any overall Type I Error rate = 0.05. Statistical inference will be made on the two secondary endpoints only if the primary endpoint demonstrates statistical significance in favor of NCX 4251. Exploratory endpoints will not be adjusted for multiplicity.

4. Study Design and Procedures

4.1 General Study Design

This is a multi-center, randomized, double-masked, placebo-controlled, Phase 2b study. Subjects will be assessed for initial eligibility at the Screening Visit (Day -14 to -7). Eligible adult subjects with a documented history of blepharitis and who are experiencing an acute exacerbation of blepharitis defined as a minimum score of “1” (on a 4-point scale) for each of Eyelid Margin Redness, Eyelid Debris, and overall Eyelid Discomfort [redacted] at both the Screening and Baseline/Day 1 Visits may be randomized into the study.

Study medication will be applied via a sterile applicator to the upper and lower eyelids and lower eyelid margin of both eyes once daily (QD) in the morning for 14 days. Subjects will also perform daily scrubs of the upper and lower eyelids of both eyes using diluted baby shampoo on a cotton swab prior to the application of the study medication.

Study visits will be as follows:

- Screening (Day -14 to -7)
- Baseline/Day 1
- Day 4 (± 1 day)
- Day 8 (± 1 day)
- Day 11 (± 1 day)
- Day 15 (- 1 day)
- Day 29/Exit (± 2 days; follow up visit)

Following the Screening Visit and prior to Baseline/Day 1 Visit, subjects will continue their previous routine for cleaning of eyelids that they were using prior to the Screening Visit. Both eyes will be treated from the Baseline/Day 1 Visit through the day prior to the Day 15 Visit. [redacted] From the Day 15 Visit through the day prior to the Day 29/Exit Visit, subjects will continue performing the eyelid scrubs.

Study medication will be self-administered topically in the morning. Morning eyelid scrubs and morning study medication application will be performed by the subject at the clinical site on the days of study visits.

A subject will be considered as having completed the study after completion of Day 29/Exit Visit (± 2 days). The duration of subject participation (from the Screening Visit to the Day 29/Exit Visit) is approximately 6 weeks. The overall study duration is estimated to be approximately 12 months from the first subject enrolled until completion of the last subject.

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in Appendix A.

5. Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

Subjects must meet all qualification criteria prior to randomization at the Baseline/Day 1 Visit. A total of approximately 300 subjects will be screened such that 200 eligible subjects will be randomized in a 1:1 ratio to receive NCX 4251 Ophthalmic Suspension, 0.1% or placebo for both eyelids, QD. [redacted]

5.2 Masking and Unmasking

The subjects, investigators, the Sponsor, the Medical Monitor, and the [redacted] interacting with the clinical sites (or handling study data) will be masked to the treatment assignment. During study visits Investigators, the Sponsor, the Medical Monitor, and masked CRO personnel interacting with the clinical sites must not be present during the instruction and supervision of study medication application. Instruction and supervision of subjects on the application of study medication will be performed by unmasked site

personnel who will not perform any other study assessments.

6. Sample Size and Power Considerations

The sample size was based on the primary endpoint of complete cure (Score 0) in the composite (sum) score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort at Day 15. For the complete cure endpoint, [redacted], approximately 208 subjects randomized overall (~104 subjects randomized per treatment group, with 94 subjects per treatment group completing the Day 15 Visit study time point evaluations) [redacted] to demonstrate statistical superiority to placebo.

The above analysis assumes a Day 15 Visit time point, [redacted], and a two-sided significance level of 5% using a Fisher's exact test.

7. Data Preparation

7.1 Input Data

All reported study data will be recorded on the electronic case report forms (eCRFs) [redacted] Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor [redacted]

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

- All data management requirements are met according to [redacted], including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by [redacted]
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

Please note that the database must be locked and all protocol deviations adjudicated as either major or minor prior to unmasking.

7.2 Output Data

Data will be transferred to [redacted] into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model

(ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM Version 1.7 model and will be implemented using the SDTM Implementation Guide Version 3.3 and the most recent SDTM Controlled Terminology version at the initiation of programming. ADaM data will follow the ADaM Version 2.1 model and will be implemented using the ADaM Implementation Guide Version 1.2. [redacted]
Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

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

8. Analysis Populations

8.1 Intent-to-Treat

The Intent-to-Treat (ITT) population includes all randomized subjects. All efficacy analyses will be performed on the ITT population, and subjects will be analyzed as randomized.

8.2 Per Protocol

The Per-Protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations likely to seriously affect the efficacy measures of the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated. The t-test analyses on the composite score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort will be conducted using the PP population as an additional analysis to assess efficacy when subjects strictly comply with the protocol. In the event that the ITT and PP populations are the same, this analyses will not be performed.

8.3 Safety

The Safety population includes all randomized subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

9. General Statistical Considerations

9.1 Unit of Analysis

The unit of analysis for the final analysis in this study will be the study eye, fellow eye for all summaries of efficacy and ocular safety assessments performed by eye (visual acuity, slit lamp biomicroscopy, intraocular pressure [IOP], dilated ophthalmoscopy). The study eye will be the eye with the highest composite score in Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort before eyelid scrubs at the Baseline/Day 1 study visit, or the right eye (OD) if both eyes of a subject have the same score at baseline. [redacted]
Additionally, AEs, medical history, and concomitant medications will be presented at the subject level.

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[redacted]

9.2 Missing or Inconclusive Data Handling

Efficacy analyses will be based on eyelid signs and symptoms (Eyelid Margin Redness, Eyelid Debris, Eyelid Discomfort). These analyses will be based on the ITT population with observed data only. To check for robustness of outcomes, [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

All AEs with completely missing onset dates will be considered treatment-emergent. All AEs with a missing month and day of onset will be considered treatment-emergent unless the onset year is prior to the year of first dose of study treatment. All AEs with a missing day of onset will be considered treatment-emergent unless (1) the onset year is prior to the first dose of study treatment or (2) the onset year is the same as the year of first dose of study treatment and the onset month is prior to the month of first dose of study treatment. All AEs missing a relationship will be considered treatment-related. Medications with missing start dates will be considered concomitant medications unless (1) the medication start year is prior to the year of the first dose of study treatment or (2) the medication start year is the same as the year of first dose of study treatment and the medication start month is prior to the month of first dose of study treatment, in which case these will be considered prior (and possibly concomitant depending on the end date) medications. Medications with missing end dates will be considered concomitant medications unless (1) the medication end year is prior to the year of first dose of study treatment or (2) the medication end year is the same as the year of first dose of study treatment and the medication end month is prior to the month of first dose of study treatment, in which case these will be considered prior medications. In the event that a medication end date is prior to the medication start date, the medication end date will be considered as one day after the medication start date for the purposes of determining whether this is a prior and/or concomitant medication. The actual reported AE onset dates and medication start and end dates, including any unknown portions, will be included in the appropriate listings as entered by site personnel.

9.3 Definition of Baseline

All on-site efficacy assessments including Eyelid signs and symptoms (Eyelid Discomfort, Eyelid Margin Redness, and Eyelid Debris) will be conducted [redacted], therefore the Baseline measure will be defined as the last non-missing measure prior to initiation of study treatment.

9.4 Data Analysis Conventions

The final analysis will [redacted] after the study is completed and the database has been locked and released for unmasking.

Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified.

Change from baseline will be provided as summaries for continuous and ordinal efficacy variables (Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort, along with the composite scores; Fluorescein Staining; [redacted] and VAS Eye Dryness, [redacted]

Summaries for continuous variables will include the number of observations (n), arithmetic mean, standard deviation (SD), standard error of the mean (SEM), 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 and SEMs will be presented to two additional decimal places than reported in the raw values. Summaries for discrete and ordinal efficacy variables (Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort, along with the composite score) will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). For continuous variables, the differences between active treatment groups and placebo will be calculated as Active – Placebo using descriptive statistics and two-sample Student's t-distribution confidence intervals (CIs) and p-values. Within one group, change from baseline will be calculated as Follow-up Visit – Baseline using descriptive statistics and one-sample Student's t-distribution CIs and p-values; differences in mean change from baseline scores between treatment groups will be summarized including 95% t-distribution CIs around the differences in mean.

Summaries will be presented for each post-baseline visit. For discrete variables, binomial proportions and Clopper-Pearson CIs will be used to compare follow-up visit to baseline within each treatment group; Fisher's exact test will be used to compare the categorical endpoints between treatment groups.

All assessments will be summarized separately by study eye and fellow eye.

Confidence intervals for differences between treatment groups will be two-sided at 95% confidence. The p-values may also be presented for change from baseline values; however, the study is not powered to show

significance for these.

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

9.5 Adjustments for Multiplicity

Statistical inference will be made on the two secondary endpoints only if the primary endpoint demonstrates statistical significance in favor of NCX 4251. Multiplicity correction within the two secondary efficacy endpoints will be completed using Hochberg's procedure.

10. 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. Subjects who complete the Day 29/Exit Visit will be considered study completers. Disposition will be summarized by treatment group and for all subjects.

The total number of screened subjects with the number and percentage of screen failure subjects will be summarized. The reasons for screen failure will be displayed with the percentages calculated using total number of screen failures as the denominator. 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.

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, lost to follow-up, Investigator decision, protocol violation, lack of compliance, study terminated by Sponsor, withdrawal by subject, and other. A subject listing will be provided that includes the date of and reason for premature study discontinuation and masking/unmasking information.

The number and percentage of subjects with major protocol deviations will be summarized by treatment group for all randomized subjects. The protocol deviations that will be summarized include: informed consent, inclusion/exclusion and randomization, test article/study drug instillation and assignment at site, improper protocol procedures at site (missed, repeated, not per protocol), site's failure to report serious adverse event (SAE)/AE, visit out of window, subject's non-compliance with test article/study drug, subject's use of prohibited concomitant medication, subject's failure to follow instructions, and other. A subject listing will be provided that includes the date of the deviation, the deviation code, the deviation description, and the classification of whether the deviation was judged to be major or minor.

In addition, subject listings will be provided that include informed consent date, inclusion and exclusion criteria violations, and exclusions from each population.

11. Demographic and Pre-treatment Variables

11.1 Demographic Variables

The demographic variables collected in this study include age, gender (including childbearing potential for female subjects), 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 the ITT and Safety populations, separately.

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

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

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

11.2 Baseline Characteristics

The following screening visit assessments will be summarized by study eye and all eyes using the appropriate set of statistics in the ITT population: [redacted] Eyelid Margin Redness Scale, Eyelid Debris Scale, Conjunctival Redness Scale, [redacted] fluorescein staining, [redacted]; slit lamp biomicroscopy eyelid, conjunctiva, cornea, lens, iris, pupil, and anterior chamber assessments; [redacted] IOP; and dilated ophthalmoscopy vitreous, retina, macula, choroid, and optic nerve assessments along with cup-to-disc ratio in the horizontal and vertical dimensions. Further details about these assessments are given later in the SAP.

A subject listing that includes all pre-treatment variables will be provided.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23,1.

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. Ocular medical history will be similarly summarized at the subject level. 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.

Listings of medical history will be generated separately for ocular and non-ocular data.

[redacted]

12.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global (B3, 01 September 2020) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, 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."

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug.

Concomitant medications will be summarized using the ITT population separately for ocular and non-ocular data. Medications will be tabulated for each treatment group 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 prior and concomitant medications will be generated separately for ocular and non-ocular medications.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

$$\text{Compliance (\%)} = \frac{\text{Number of Doses Received}}{\text{Number of Expected Doses}} \times 100\%$$

The number of doses received will be determined through a review of the subject diary and the in-office applications.

[redacted]

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group, using the ITT population. The compliance category defined above will be summarized with discrete summary statistics.

A subject listing of dosing compliance will also be produced.

13.2 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 Baseline/Day 1 Visit) + 1

Extent of treatment exposure for subjects who were lost to follow-up will be calculated in days using the following:

Extent of Exposure (days) = (Date of Last Recorded Visit – Date of Baseline/Day 1 Visit) + 1

A subject listing of treatment exposure will be produced.

14. Efficacy Analyses

All assessments will be conducted by the Study Eye [redacted]

14.1 Efficacy Endpoints

Primary

- Proportion of subjects who achieve a Complete Cure (score of 0) by Day 15 in all of the following scores Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort

Secondary

- Mean change from baseline in the Eye Dryness Symptoms using the VAS at the Day 15 Visit
- Mean change from baseline in the Fluorescein Staining of the inferior cornea at the Day 15 Visit

14.2 Eye Assessments Used for the Efficacy Endpoints

14.2.1 [redacted] Eyelid Discomfort

[redacted] Eyelid Discomfort is subject-reported based on a four-point scale [redacted]

14.2.2 [redacted] Eyelid Margin Redness

After assessing Eyelid Discomfort, the Investigator assesses and grades Eyelid Margin Redness based on the following four-point scale: [redacted]

14.2.3 [redacted] Eyelid Debris

After accessing Eyelid Discomfort and Eyelid Margin Redness, the Investigator assesses and grades Eyelid Debris based on the following four-point scale: [redacted]

14.2.4 Composite Score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort

The composite score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort is defined as the sum across the three measurements at a particular visit. If any of the assessments is missing, the composite score will be set to missing.

14.2.5 Eye Dryness Symptoms [redacted]

Eye Dryness Symptoms are self-reported using a 0-100 mm VAS, where 0 = No Discomfort and 100 = Maximal Discomfort. [redacted]

14.2.6 Fluorescein Staining

Fluorescein staining is Investigator assessed using a 5-point scale (allowing for half interval responses) [redacted]

14.3 Detailed Description of the Efficacy Analysis

Complete cure (Score 0) in the composite (sum) of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort will be summarized using discrete summary statistics (frequency counts and percentages) as well as two-sided 95% Clopper-Pearson CIs by treatment group. The primary efficacy analyses will test the difference in the proportion of study eyes with complete cure in the composite score between NCX 4251 Ophthalmic Suspension and placebo at Day 15 [redacted]. The marginal proportions and difference in proportions along with the corresponding two-sided 95% CIs and p-value will be presented.

Secondarily, differences (NCX 4251 Ophthalmic Suspension minus placebo) between treatment groups will be summarized using difference in proportions, 95% asymptotic CIs around the differences in proportions, and Pearson's chi-squared test. Summaries will be presented for the Day 15 Visit [redacted]

Change from baseline in the composite (sum) score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort will be summarized using continuous summary statistics (n, mean, SD, standard error, median, minimum and maximum) as well as two-sided 95% t-distribution CIs by treatment group. Additionally, differences in mean change from baseline scores (NCX 4251 Ophthalmic Suspension minus placebo) between treatment groups will be summarized including 95% t-distribution CIs around the differences in mean. Summaries will be presented for the Day 15 Visit as well as each other post-baseline visit.

[redacted]

[redacted]

Secondary endpoints will be summarized using continuous summary statistics (n, mean, SD, standard error, median, minimum, and maximum) as well as two-sided 95% t-distribution CIs around the mean by treatment group. The primary analysis of the secondary endpoints will employ a linear model with mean change from baseline in Eye Dryness evaluated on the VAS and mean change from baseline in Fluorescein Staining of the inferior cornea at the Day 15 Visit as the response and baseline eye dryness as a covariate. Least squared means and differences between treatment groups, along with corresponding 95% CIs and p-values will be presented. [redacted] Secondary analyses of the secondary endpoints will include two-sample t-tests and 95% t-distribution CIs for the difference in means.

[redacted]

All efficacy endpoint values will be included in listings.

[redacted]

[redacted]

15. [redacted]

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16. Safety Analyses

All safety analyses will be conducted using the Safety population.

16.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Lack of efficacy will be reported as a treatment failure, not as an AE.

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. Adverse events recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

The severity of an AE should be categorized as mild, moderate, or severe per Investigator's judgment with the following scale in consideration:

- **Mild**: Awareness of a sign or symptom that does not interfere with the subject's usual activities or is transient, resolved without treatment and with no sequelae
- **Moderate**: Interferes with the subject's usual activities, and/or requires symptomatic treatment
- **Severe**: Symptom(s) causing severe discomfort and significant impact of the subject's usual activities and requires treatment

Adverse events with a missing severity will be counted as severe.

A determination of the relationship between an AE and the study medication must be made by the Investigator for each AE. The following terms to evaluate the causality of the AE with the study drug should be used:

- **Unrelated**: A simultaneous disease, a simultaneous treatment or any other known cause is clearly

responsible for the safety event and the AE is not related to the study medication.

- **Unlikely**: On the basis of the available knowledge regarding the subject's history, the disease process, the timing of the safety event in relation to the application of the study medication and the mode of action of study medication, a relation between the study medication and the safety event is unlikely, but cannot be totally excluded.
- **Possible**: This relation exists when the safety event follows the reasonable chronological sequence from the moment of the study medication application, but when the safety event could also have been caused by the clinical condition of the subject or by other treatment administered to the subject.
- **Probable**: This relation exists when the safety event follows a reasonable chronological sequence from the moment of the study medication application, corresponds to a known effect of the study medication, is confirmed by the observation of an improvement upon discontinuation of the study medication application, and therefore the study medication is the most probable of all the causes.
- **Definite**: This relation exists when the safety event follows a reasonable chronological sequence from the moment of the study medication application, corresponds to a known effect of the category of the studied medication, is confirmed by the observation of an improvement upon discontinuation of the study medication, and no other reasonable cause exists.

Treatment-emergent adverse events possibly, probably, or definitely related to study drug will be considered treatment-related TEAEs. Any TEAEs with a missing relationship will be considered treatment-related TEAEs.

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Results in-subject hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- Results in life-threatening illness or injury (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe, or had continued untreated); or
- Results in a significant and persistent loss or impairment of vision.

Additionally, medical events that may not meet these criteria may be considered an SAE if, based on the medical judgment of the Investigator, such medical events may require an intervention to prevent any of the outcomes listed above.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one AE and TEAE, by treatment group and over all subjects. This

summary will also include breakdowns of TEAEs further categorized as treatment-related TEAEs, SAEs, TEAEs leading to early treatment discontinuation, TEAEs leading to death, and TEAEs by maximum severity.

Additional summaries of TEAEs will be provided showing the number of events and the number and percentage of subjects who experienced at least one TEAE by treatment group and over all subjects. Ocular and non-ocular TEAEs will be summarized together using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT. 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, SOCs will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Separate summaries will be provided for the following categories of AEs:

- Treatment-Related TEAEs
- TEAEs by Relationship to Study Drug
- TEAEs by Maximal Severity

The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximum severity.

All AEs will be presented in a subject listing. The TEAEs leading to study treatment discontinuation will be listed separately. In addition, all SAEs will be presented in a separate listing.

16.2 Best Corrected Visual Acuity

Best corrected visual acuity will be measured by trained personnel prior to slit-lamp examination and dilating the eyes, with the subject wearing their habitual correction or with pinhole refraction.

Testing of both eyes is done at a distance of 4 meters from the visual acuity Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. The chart should be at a comfortable viewing angle. The right eye (chart 1) will be tested first then the left eye (chart 2). The eye not being tested will be properly occluded.

The observed and change from baseline BCVA will be summarized using continuous descriptive statistics by visit for each treatment group and for all actively treated subjects. A subject listing of BCVA will be produced. [redacted]

16.3 Intraocular Pressure

Intraocular pressure will be measured by qualified study site personnel at each specified visit using a Goldmann applanation tonometer affixed to a slit lamp and in accordance with the site's standard practice.

Two measurements will be obtained, and the mean of the two readings will be calculated and recorded. If the first two measurements differ by more than 2 mmHg, a third measurement will be obtained and the median IOP will be recorded.

The IOP values and changes from baseline for each eye (study eye and all eyes) will be summarized using continuous descriptive statistics by visit and eye for each treatment group and for all actively treated subjects. A subject listing of IOP will also be produced.

16.4 Slit Lamp Biomicroscopy

The slit lamp examination will be performed prior to any contact assessments and instillation of any drops at each specified visit.

Each structure will be graded [redacted] The following structures will be examined at each visit: cornea, conjunctiva [redacted] anterior chamber, iris, lens, eyelid (other than Eyelid Margin Redness and Eyelid Debris), and pupil.

A subject listing of the slit lamp biomicroscopy parameters will also be produced.

17. Interim Analyses

There are no planned interim analyses for this study.

18. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

19. References

SAS Online documentation (http://support.sas.com/kb/63/038.html).

20. Revision History

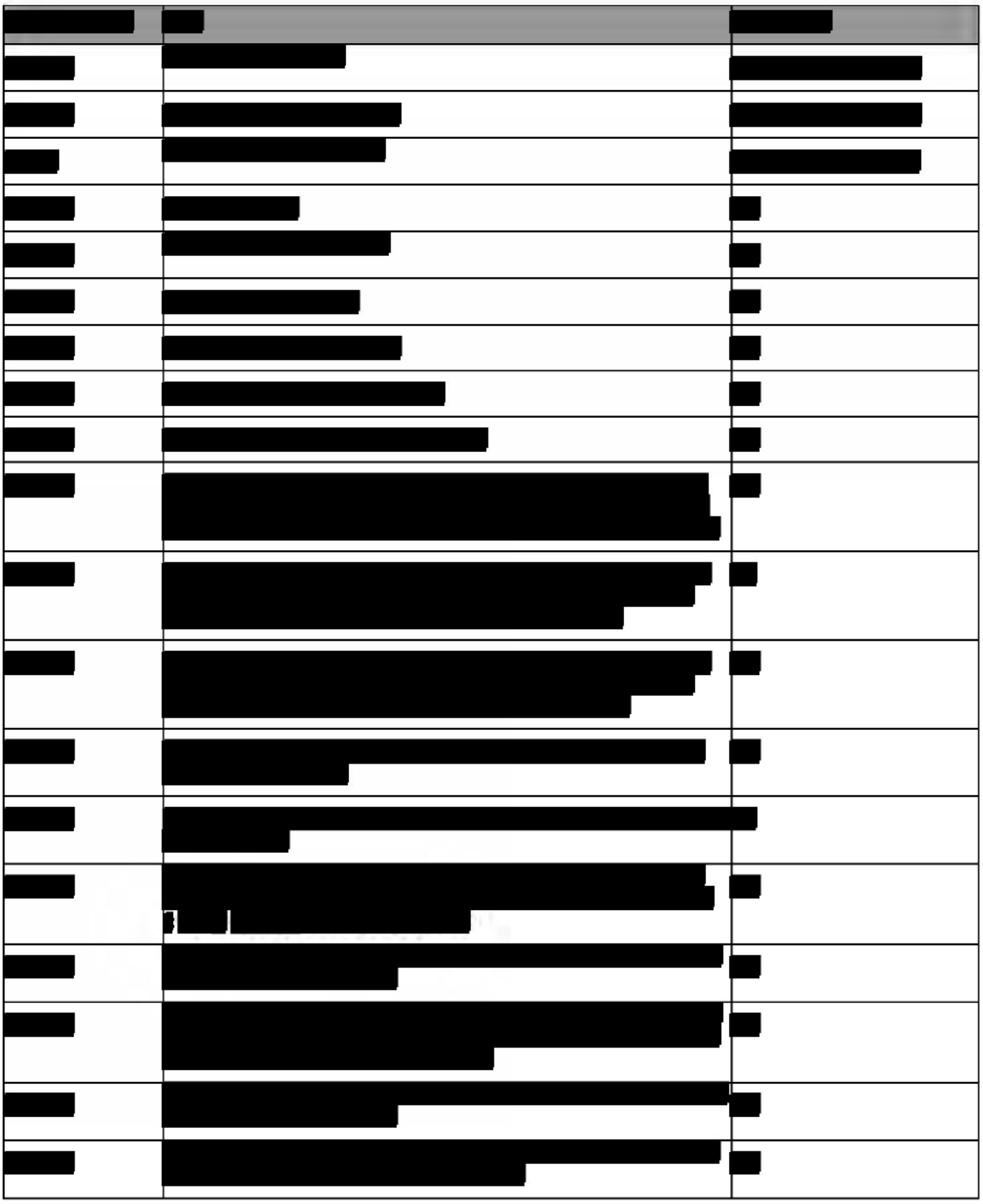
A revision was issued (version 2.0) on August 4, 2021.

Summary of Changes

Section #	Description of Change	Rationale
14.3	Provide clarification on the [redacted]	[redacted]

21. Tables

The following tables are planned to be included in the final analysis. Tables to be included in the topline analysis are highlighted below in bold.



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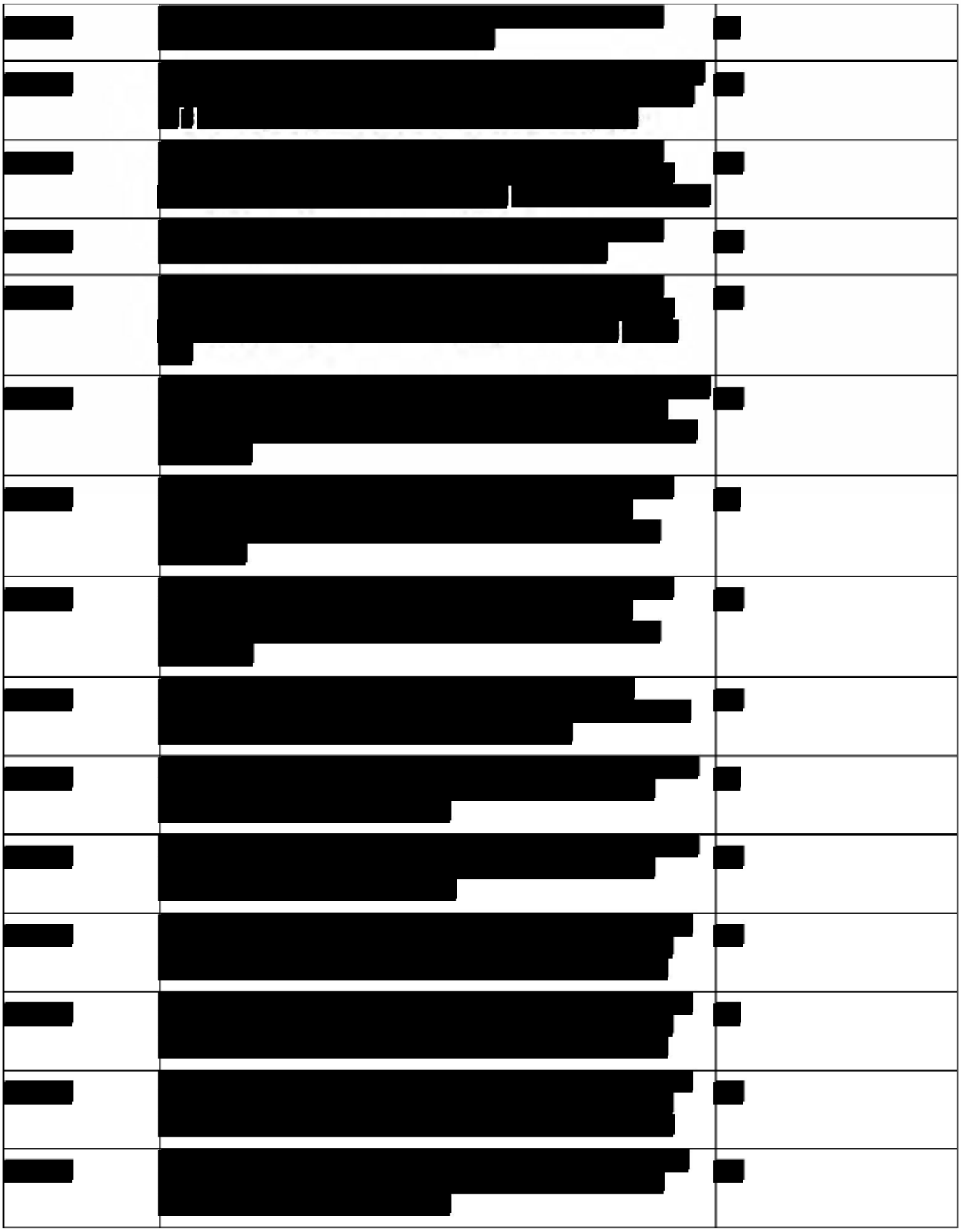

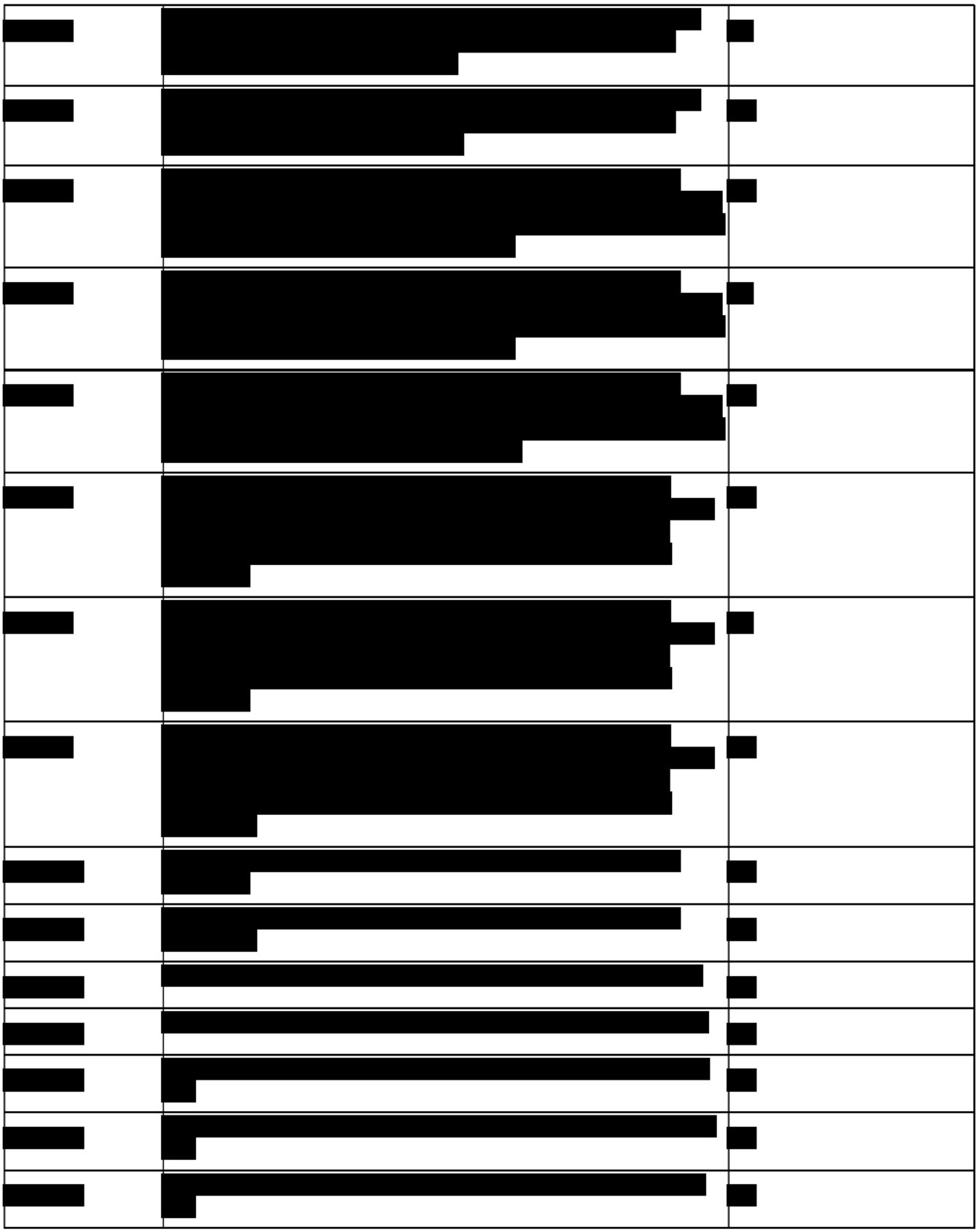

[redacted]

[redacted]		
14.3.1	**Overall Summary of TEAEs**	Safety
14.3.2	**TEAEs by System Organ Class and Preferred Term**	Safety
14.3.3	Treatment-Related TEAEs by System Organ Class and Preferred Term	Safety
14.3.4	TEAEs by System Organ Class, Preferred Term, and Relationship to Study Drug	Safety
14.3.5	TEAEs by System Organ Class, Preferred Term, and Maximal Severity	Safety
14.3.6	Best Corrected Visual Acuity (logMAR)	Safety
14.3.7.1	Intraocular Pressure (mmHg)	Safety
14.3.7.2	Intraocular Pressure (mmHg) Categorical Changes from Baseline	Safety
14.3.8.1	Slit Lamp Biomicroscopy	Safety
14.3.8.2	Slit Lamp Biomicroscopy – Shift from Baseline	Safety
14.3.9.1	Dilated Ophthalmoscopy	Safety
14.3.9.2	Dilated Ophthalmoscopy– Shift from Baseline	Safety
14.3.10	Treatment Compliance and Exposure	Safety

22. Listings

Listing Number	Title
16.1.7	Randomization
16.2.1	Subject Disposition
16.2.2	Protocol Deviations
16.2.3.1	Inclusion/Exclusions Criteria
16.2.3.2	Analysis Populations

16.2.4.1	Demographics
16.2.4.2	Baseline Characteristics
16.2.4.3	Ocular Medical History
16.2.4.4	Non-Ocular Medical History
16.2.4.5	Prior and Concomitant Ocular Medications
16.2.4.6	Prior and Concomitant Non-Ocular Medications
16.2.5	Study Drug Administration
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
16.2.7.1	All Adverse Events
16.2.7.2	Adverse Events Leading to Study Drug Discontinuation
16.2.7.3	Serious Adverse Events
16.2.7.4	Best-Corrected Visual Acuity (BCVA) at 4 Meters (logMAR)
16.2.7.5	Intraocular Pressure (IOP)
16.2.7.6	Slit Lamp Biomicroscopy
16.2.7.7	Dilated Ophthalmoscopy
16.2.8	Urine Pregnancy Test

[redacted]

Appendix A

Table 1. Schedule of Visits and Assessments

[redacted]

Review of Subject Diary	-	-	X	X	X	X	-
Collection of Study Medication and Diary	-	-	-	-	-	X	-
Eyelid Scrub & Study Medication Application Training	-	X	-	-	-	-	-
Adverse Event Query	X	X	X	X	X	X	X
Study Exit	-	-	-	-	-	-	X

a) Screening Visit may be performed at any time of the day.
b) Subject-rated eyelid discomfort will be assessed prior to investigator-evaluated eyelid margin redness and eyelid debris.
c) Daily eyelid scrubs will be performed prior to study medication application by the subject when self-administering study treatment. On study visit days eyelid scrubs and study medication application will be performed by the subject under the supervision of the study staff.
d) At the Baseline/Day 1 Visit, study medication is administered by the subject after site confirmation of eligibility and randomization. Subjects will be instructed on proper application technique.