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FINAL STATISTICAL ANALYSIS PLAN FOR NCX 4251-01 PHASE 2 CLINICAL STUDY

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

Sponsor: Nicox Ophthalmics, Inc.

Protocol Number: NCX-4251-01

Author: [redacted]

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Statistical Analysis Plan Approval

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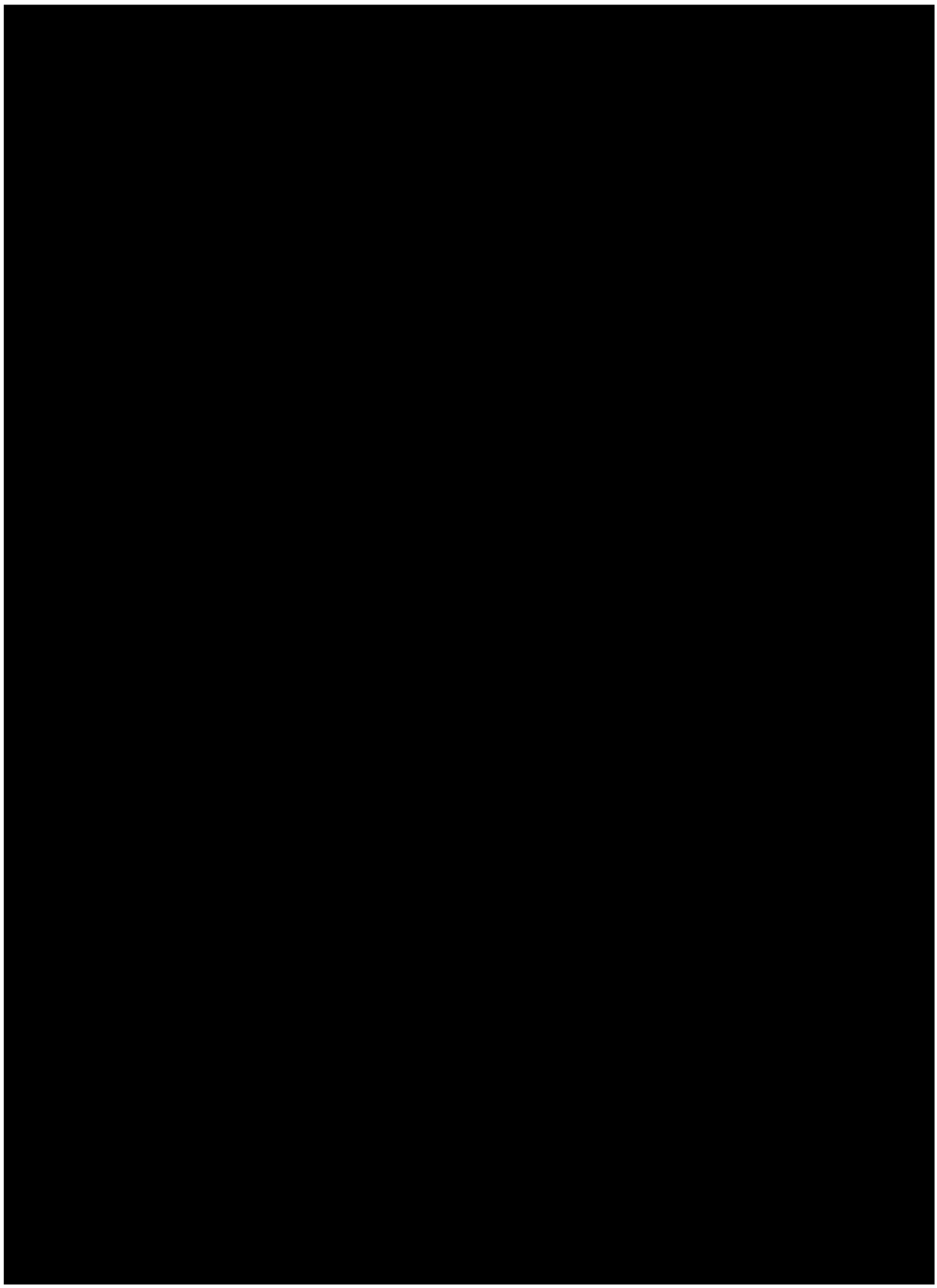

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List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BID	*Bis In Die* (Twice Daily)
CI	Confidence Interval
[redacted]	[redacted]
Ecrf	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
GEE	Generalized Estimating Equations
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
OD	*Oculus Dextrus* (Right Eye)
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
SDC	Statistics & Data Corporation
SEM	Standard Error of the Mean
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
[redacted]	[redacted]
[redacted]	[redacted]
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-4251-01, version 5.0 dated 13 Aug 2019. [redacted]

[redacted] the combined analyses for Cohort 1 and Cohort 2 analysed together will be covered in the body of this "Final Statistical Analysis Plan for NCX 4251-01 Phase 2 Clinical Study" and carried out following database lock and unmasking of the Cohort 2 portion of the NCX 4251-01 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

Primary Objective

The primary objective of this clinical study is to select the dose(s) of NCX 4251 to be advanced into the next stage of development.

Secondary Objectives

The secondary objectives of the study are to assess the safety and tolerability of the study medication applied once daily (QD) and twice daily (BID).

2.1 Study Variables

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

- Eyelid signs and symptoms (Eyelid Debris, Eyelid Margin Redness, and Eyelid Discomfort)
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Intraocular pressure (IOP)
- Dilated ophthalmoscopy
- Best-corrected visual acuity (BCVA)
- Urine pregnancy tests (for females of childbearing potential)
- Adverse Events (AE)

2.2 Efficacy Endpoints

The efficacy endpoints are the following for Cohort 1 and 2. [redacted]

- Mean change from baseline in composite (sum) score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

2.3 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

[redacted]

[redacted]

2.5 Statistical Hypotheses

There are no formal hypotheses in this early phase study.

3 Study Design and Procedures

3.1 General Study Design

This is a multi-center, randomized, double-masked, placebo-controlled, dose-escalation study consisting of two cohorts, Cohort 1 and Cohort 2 studied sequentially. Each cohort consists of two arms, placebo and NCX 4251 Ophthalmic Suspension 0.1%. Approximately 15 subjects in Cohort 1 will be randomized in a 2:1 ratio (NCX 4251:placebo) and will receive study medication QD. [redacted] Approximately 20 subjects in Cohort 2 will be randomized in a 1:1 ratio and will receive study medication BID. Screening of eligible subjects for Cohort 2 will commence after the interim analysis from the Cohort 1 is conducted.

In each cohort, subjects will be assessed for initial eligibility at the Screening Visit (Day -7 to -3). Eligible adult subjects with a 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 will be randomized into the study.

For both Cohorts 1 and 2, study visits will be as follows: Screening (Day -7 to -3), Baseline/Day 1, Day 4 (± 1 day), Day 8 (± 1 day), Day 11 (± 1 day), Day 14 (- 1 day; last day of treatment), and Day 28/Exit (± 2 days; follow-up visit).

Following the Screening Visit prior to Baseline/Day 1 Visit, subjects will continue their previous routine for cleaning of eyelids that they were using prior to Screening Visit. Both eyes will be treated from the Baseline/Day 1 Visit through Day 14 Visit. The study eye will be the eye with the highest composite score before eyelid scrubs at Baseline/Day 1 or the right eye (OD) if both eyes of a subject have the same score at baseline. The contralateral eye will be considered as the fellow eye. After the Day 14 Visit, subjects will continue using the eyelid scrubs per instructions provided in the study protocol until the day prior to the Day 28/Exit Visit.

Study medication will be self-administered topically in the morning (Cohort 1), or in the morning and evening (Cohort 2). Morning eyelid scrubs and morning study medication application will be performed by the subject at the clinical site on the days of study visits under supervision of the study personnel.

A subject will be considered as having completed the study after completion of Day 28/Exit Visit (± 2 days). The duration of subject participation (from the Screening Visit to the Exit Visit) is approximately 5 weeks.

The overall study duration is estimated to be approximately 6 months from the first subject enrolled until completion of the last subject.

The study design is essentially identical for Cohort 1 and Cohort 2; the main differences are the dosing frequency (QD vs. BID), the randomization ratio (2:1 vs 1:1), [redacted]

3.2 Schedule of Visits and Assessments

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

4 Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, subjects who provide verbal and written informed consent will be assigned a unique 5-digit subject ID, which consists of the 2-digit site number plus a unique 3-digit screening number (beginning with 001 within each site). A subject must meet all qualification criteria at the Baseline/Day 1 Visit to be randomized. Approximately 15 subjects in Cohort 1 will be randomly assigned to NCX 4251 0.1% QD or placebo QD in a 2:1 ratio. Approximately 20 subjects in Cohort 2 will be randomly assigned to NCX 4251 0.1% BID or placebo BID in a 1:1 ratio. Study drug will be randomly assigned using a (2:1 for Cohort 1, 1:1 for Cohort 2) assignment ratio, which is stratified by site. Sequentially numbered study drug kits will be provided to each investigational site, in accordance with the site-specific randomized study drug kit list, which consists of sequential 4-digit kit ID numbers. Subjects who meet all eligibility criteria will be randomized by assignment of the lowest 4-digit study drug kit number available at their investigational site. If a randomized subject is discontinued from the study for any reason, their randomized study drug kit number will not be reassigned. A back-up block of treatments will be available at each site to be used for study treatment replacement.

The 5-digit subject ID will be used to identify subjects in all datasets and listings for this study.

4.2 Masking and Unmasking

The study statistician will generate the complete randomized study drug kit list. The subject, Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the study.

[redacted].

If unmasking of a subject becomes critical to the subject's safety, the Principal Investigator must authorize such decision. If possible, such decision must be first consulted with both the study Sponsor and the Medical Monitor. Unmasking can be achieved by opening the sealed envelope that corresponds to the randomization number assigned to the subject. 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

The sample size was not calculated to yield pre-stated power for a specific efficacy analysis; instead, the sample size in this early phase study will assist in obtaining estimates from which to power future studies.

6 Data Preparation

6.1 Input Data

All reported study data will be recorded on the eCRF [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 [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 [redacted] Sponsor personnel.
- 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.

6.2 Output Data

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

[redacted]

7 Analysis Populations

7.1 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.

7.2 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.

7.3 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.

8 General Statistical Considerations

8.1 Unit of Analysis

The unit of analysis for the final analysis in this study will be the study eye, fellow eye, and both eyes for all summaries of efficacy and ocular safety assessments performed by eye (VA, SLE, IOP, dilated ophthalmoscopy). The study eye will be the eye with the highest composite score in Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort [redacted] at the Baseline/Day 1 study visit, or the right eye (OD) if both eyes of a subject have the same score at baseline. The contralateral eye will be considered as the fellow eye; however, no analyses will be conducted specifically for the contralateral eyes. Instead as stated above, analyses by both eyes will be conducted given the bilateral nature of the dosing and the inclusion criteria requiring both eyes to qualify. Additionally, AEs, medical history, and concomitant medications will be presented at the subject level.

8.2 Missing or Inconclusive Data Handling

Efficacy analyses will be primarily based on the ITT population with observed data only. To check for robustness of outcomes, missing data will be imputed using last time consistent (pre- and post-eyelid scrub) observation carried forward for the composite endpoint analysis by eye.

AEs with completely missing onset dates will be considered treatment-emergent. 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. 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. 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.

8.3 Definition of Baseline

Eyelid signs and symptoms (Eyelid discomfort, Eyelid Margin Redness and Eyelid Debris) were conducted [redacted]. The analysis of the response to treatment of eyelid signs and symptoms will involve comparisons against the [redacted] baseline assessments. For all other assessments [redacted] the Baseline measure will be defined as the last non-missing measure prior to initiation of study treatment.

8.4 Data Analysis Conventions

The final analysis including Cohorts 1 and 2 will be performed [redacted] after the study is completed and the database has been locked and released for unmasking of Cohort 2, and the statistical analysis plan has been finalized. [redacted] In addition, the final analysis will pool results from both Cohort 1 and Cohort 2 for some endpointsas applicable.. Data to be pooled includes the following:

- Subject Disposition
- Demographics
- Baseline Characteristics
- [redacted]

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

Change from baseline will be provided as summaries for continuous and ordinal efficacy (Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort, along with the composite scores; [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 standard errors of the mean will be presented to two additional decimal places than reported in the raw values. Summaries for discrete and ordinal efficacy (Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort, along with the composite score) variables 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 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. These summaries will be completed separately for the pre-scrub and post-scrub assessments. 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 by study eye, fellow eye, and by both eyes, unless specifically stated. When the assessments need to be presented in both eyes, for continuous variables, between group CIs and p-values will come from a mixed effects linear model for each post-baseline visit

Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. 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.

8.5 Adjustments for Multiplicity

No adjustments for multiplicity will be made for this early phase study.

9 Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the study, and discontinued from the study. Subjects who complete the Day 28/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. 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, physician decision, protocol violation, 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, no 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.

10 Demographic and Pre-treatment Variables

10.1 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.

10.2 Baseline Characteristics

[redacted] 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] BCVA; [redacted] Eyelid Margin Redness Scale, Eyelid Debris Scale, [redacted], [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.

11 Medical History and Concomitant Medications

11.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

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.

11.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (Global B3, March 2019) 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.

12 Dosing Compliance and Treatment Exposure

12.1 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:

$$\text{Compliance (\%)} = 100\% \times \frac{\text{Number of doses received}}{\text{Number of expected doses}}$$

The number of doses received will be determined through a review of the subject diary and the in-office applications. The number of expected doses is 14 for subjects assigned to Cohort 1 and 28 for subjects assigned to Cohort 2.

[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, including eyelid scrub data, will also be produced.

12.2 Treatment Exposure

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

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

13 Efficacy Analyses

All assessments will be conducted by the Study Eye

13.2 Efficacy Endpoints

The efficacy endpoints will be evaluated with respect to the Study Eye,

-
-
-

The following endpoints will be evaluated with respect to the Study Eye

-
- Mean change from baseline in Composite (Sum) Score of Eyelid Margin Redness, Eyelid Debris, and Eyelid Discomfort
-
-
-

[redacted]

- [redacted]
- [redacted]

[redacted]

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

[redacted]

13.3 Eyelid Assessments

13.3.1 [redacted] EYELID DISCOMFORT

[redacted] Eyelid Discomfort is subject-reported based on a four-point scale with responses of 0 = No eyelid discomfort, 1 = Mild [redacted], 2 = Moderate [redacted], and 3 = Severe [redacted].

13.3.2 [redacted] EYELID MARGIN REDNESS

After assessing eyelid discomfort, the Investigator assesses and grades eyelid margin redness based on the following scale: 0 = None: [redacted] 1 = Mild: [redacted] 2 = Moderate: [redacted] and 3 = Severe: [redacted]

13.3.3 [redacted] EYELID DEBRIS

After accessing eyelid discomfort and eyelid margin redness, the Investigator assesses and grades eyelid debris based on the following scale: 0 = None: [redacted] 1 = Mild: [redacted] 2 = Moderate: [redacted] 3 = Severe: [redacted]

13.3.4 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.

13.4 Detailed Description of the Efficacy Analysis

Though p-values and CIs will be displayed as described below, it is of note that the study is not powered to demonstrate statistical significance. These are only displayed as a preliminary investigational tool to aid with planning future studies. All efficacy endpoint values will be included in listings.

13.4.1 [redacted] Eyelid Discomfort

[redacted] Baseline to All Follow-up Eyelid Scrubs for Study Eye:

Within each treatment group, Eyelid Discomfort at the [redacted] baseline and follow-up visits ([redacted] will be tabulated using continuous summary statistics (n, median, standard deviation, median, minimum and maximum); one-sample Student's t-distribution CIs and p-values will be used for comparing change from baseline to follow-up visits. Between treatment groups, two-sample Student's t-distribution CIs and p-values are calculated to compare the Eyelid Discomfort scores at each visit as well as the change from baseline.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]s;

RUN;

[redacted]

[redacted]

[redacted]

13.4.4 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.

The composite endpoint based on changes from baseline [redacted]

[redacted]

[redacted]

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 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 (TEAE) 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 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, serious AEs (SAE), 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 TEAEs 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.

15.2 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 ETDRS (Early Treatment of Diabetic Retinopathy Study) 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.

15.3 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.

15.4 Slit Lamp Biomicroscopy Examination

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

The following structures will be examined at each visit: eyelid (other than eyelid margin redness and eyelid debris), conjunctiva cornea, lens, iris, pupil, and anterior chamber.

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

17 Changes from Protocol Stated Analyses

The protocol describes analyses pooling just the placebo arms from Cohorts 1 and 2; however, the SAP includes analyses pooling both the placebo arms from each cohort and the NCX 4251 arms from each cohort.

The protocol describes AE summaries separately for ocular and non-ocular AEs. Given the low number of expected AEs overall, the SAP combines summaries of ocular and non-ocular AEs. The separation of AEs by SOC will clearly identify which AEs are ocular and which are not.

18 References

There are no references for this SAP.

19 Revision History

The following revisions were made to version 1.0 of the SAP, after approval of version 5.0 of the study protocol.

Section	Revision	Rationale
All	Administrative changes	To provide consistency and better readability
1	Revised to version 5.0 of the protocol	Protocol amendment
2.2 – 2.4	Revised and reordered endpoints	Protocol amendment
3.1, 4, 7.2, 8, 13.2	Updated details to match the current protocol and analysis strategy	Protocol amendment
3.2 and Appendix A	Moved the schedule of assessments to the appendix	To provide better readability in the SAP text
6.1 and 6.2	Separated Section 6 into two sections6.1 and new section 6.2; added Section 6.2 to discuss output data formats	To detail the formats of SDTM, ADaM, and associated deliverables
13.4	Added details of the analyses including both eyes and the Clopper Pearson CI calculations	To fully describe the statistical analyses for efficacy endpoints, including the statistical modeling and specific endpoints to which the analyses apply
14.2.2	Add description of the meibomian gland assessments used for Cohort and how the data will be analyzed	Protocol amendment
15.1	Added more detail about AE summaries	To provide a better explanation of the AE summaries included in the study
19	Added revision history	To document the changes from version 1.0 to version 2.0 of the SAP
20 – 21	Updated tables of contents for tables and listings	To match the planned output for the final analysis

20 Tables to Be Included In the Final Analysis

Tables to be included in the topline analysis are highlighted below.

Table Number	Title	Population
[redacted]	[redacted]	[redacted]
14.1.1.2	Subject Disposition, Cohorts 1 and 2 Combined	All Screened Subjects
14.1.1.3	Reasons for Screen Failure, Cohort 2	All Screened Subjects
14.1.2	Major Protocol Deviations, Cohort 2	All Randomized Subjects
[redacted]	[redacted]	[redacted]
14.1.3.2	Demographics, Cohorts 1 and 2 Combined	ITT
[redacted]	[redacted]	[redacted]
14.1.4.2	Baseline Characteristics, Cohorts 1 and 2 Combined	ITT
14.1.5.1	Ocular Medical History, [redacted]	ITT
14.1.5.2	Non-Ocular Medical History, [redacted]	ITT
14.1.6.1	Ocular Concomitant Medications, [redacted]	ITT
14.1.6.2	Non-Ocular Concomitant Medications, [redacted]	ITT
[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]

Table Number	Title	Population
[redacted]	[redacted]	[redacted]

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

21 Listings

Listing Number	Title
16.1.7	Randomization
16.2.1	Subject Disposition
16.2.2	Protocol Deviations
16.2.3.1	Inclusion/Exclusion 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]

Listing Number	Title
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
16.2.7.7	Best Corrected Visual Acuity (BCVA) at 4 Meters (logMAR)
16.2.7.8	Intraocular Pressure (IOP)
16.2.7.9	Slit Lamp Biomicroscopy
[redacted]	[redacted]
16.2.7.11	Dilated Ophthalmoscopy
16.2.8	Urine Pregnancy Test

[redacted]

22 Appendix A

Table 1. Schedule of Visits and Assessments

	Screening Visit[a] (day -7 to -3)	Baseline/ Day 1 Visit	Day 4 Visit (± 1 day)	Day 8 Visit (± 1 day)	Day 11 Visit (± 1 day)	Day 14 Visit (- 1 day)	Day 28/ Exit Visit (± 2 days)
Informed Consent/HIPAA	X	-	-	-	-	-	-
Screening Number and Registration	X	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-
Medical/Ophthalmic History & Update	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Urine Pregnancy Test	X	-	-	-	-	X	-
[redacted]	X	X	-	X	X	X	X
Best Corrected Visual Acuity (ETDRS)	X	X	X	X	X	X	X
Eyelid Evaluation	X	-	-	-	-	-	-
[redacted]	-	X	X	X	X	X	X
Slit Lamp Biomicroscopy	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X
[redacted]	X	X	-	-	-	X	-
[redacted]	X	X	-	X	X	X	X
[redacted]	X	X	-	X	X	X	X
[redacted]	X	X	-	X	X	X	X
IOP	X	X	X	X	X	X	X
[redacted]	-	X	X	X	X	X	X
Study Medication Application [redacted]	-	X[c]	X	X	X	X	-
[redacted]	-	X[d]	X	X	X	X	X[d]
[redacted]						X[e]	
[redacted]	X	X	-	-	-	X	-
Dilated Ophthalmoscopy	X	-	-	-	-	-	X
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-
Randomization	-	X	-	-	-	-	-
Dispense study medication, study related material, diary and instructions	-	X	-	-	-	-	-
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. All other visits will be performed in the morning with specific time points for certain assessments.*
b) *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.*
c) *At the Baseline/Day 1 Visit, study medication is administered* [redacted] *final confirmation of Eligibility and randomization. Subjects will be instructed on proper application technique. Refer to Section 7.2 of the protocol for detailed order of assessments.*

[redacted]

d) [redacted]

f) *Subject-rated eyelid discomfort will be assessed prior to investigator-evaluated eyelid margin redness and eyelid debris*