Statistical Analysis Plan for:

Phase 3 Trial of NCX 470 vs Latanoprost in Subjects with Open-Angle Glauocma or Ocular Hypertension (Mont Blanc)

NCT#04445519

06-May-2022

[redacted]

STATISTICAL ANALYSIS PLAN

A Phase 3, Randomized, Adaptive Dose-Selection, Multi-Regional, Double-Masked, Parallel-Group, 3–Month Trial Evaluating the Safety and Efficacy of NCX 470 vs. Latanoprost 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension (Mont Blanc)

Sponsor: Nicox Ophthalmics, Inc.

Protocol Number: NCX-470-02

Author: [redacted]

Date: 06MAY2022

Version: 2.0

[redacted]

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Protocol Number: **NCX-470-02**

SAP Version: **2.0**

Date: **06MAY2022**

Statistical Analysis Plan Approval

Prepared by: _____ _____

[redacted]

Reviewed by: _____ _____

[redacted]

Approved by: _____ _____

[redacted]

Approved by: _____ _____

[redacted]

[redacted]

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Abbreviation	Definition
ADaM	Analysis Data Model
ADSP	Adaptive Dose Selection Period
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
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
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
OD	*Oculus dexter* (Right Eye)
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
QD	*Quaque die* (Once Daily)
RTF	Rich Text Format
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHODrug	World Health Organization Drug Dictionary

[redacted]

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol NCX-470-02, Version 2.0 dated 08JUL2020.

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.

1.1 Update After the Adaptive Dose Selection

[redacted]

2. Study Objectives

The primary objective is to demonstrate that NCX 470 0.1% once daily (QD) is non-inferior to latanoprost 0.005% QD based on mean IOP reduction from time-matched baseline at the 8 AM and 4 PM time points at the Week 2, Week 6, and Month 3 Visits.

[redacted]

Another secondary objective is to demonstrate that NCX 470 0.1% QD is safe and well tolerated when administered to subjects for 3 months.

2.1 Study Endpoints

2.1.1 Efficacy Endpoints

The primary efficacy endpoint for this trial is mean IOP reduction from time-matched baseline (based on Eligibility 1 and Eligibility 2 Visits) at the 8 AM and 4 PM time-points at the Week 2, Week 6, and Month 3 Visits in the study eye.

The primary efficacy analysis is the non-inferiority comparison of the mean treatment effect between NCX 470 0.1% and latanoprost 0.005% in the study eye. A secondary efficacy analysis is the superiority comparison of the treatment effect between NCX 470 0.1% and latanoprost 0.005% in the study eye.

The secondary efficacy endpoints for this trial include:

2.1.2 Safety Endpoints

Safety assessments will include but not limited to:

- Treatment-emergent adverse events (TEAEs)
- Best-corrected visual acuity (BCVA)
- Slit-lamp biomicroscopy
- Conjunctival hyperemia
- Dilated ophthalmoscopy
- Pachymetry
- Intraocular pressure (IOP)
- Pupil size
- Perimetry
- Iris color
- Urine pregnancy tests for females of child-bearing potential
- Rate of discontinuation from study

2.2 Primary and Secondary Hypotheses

The primary and secondary endpoints will be tested in a hierarchical fixed sequence in the order below. The hypothesis language has been updated from the sample size and power calculations from the protocol

When testing if NCX 470 0.1% ophthalmic solution is non-inferior to latanoprost 0.005% ophthalmic solution the primary hypotheses are:

H_0: The upper bound of the 95.1% CI around the difference between study eyes treated with NCX 470 0.1% and latanoprost 0.005% (NCX 470 – latanoprost), in the time-matched IOP reduction from baseline (follow-up minus baseline) is > 1.5 mmHg for at least one of the 6 time points (Week 2, 8 AM and 4 PM; Week 6, 8 AM and 4 PM; Month 3, 8 AM and 4 PM) or > 1.0 at least 3 of the 6 time points.

H_A: The upper bound of the 95.1% CI around the difference between study eyes treated with NCX 470 0.1% and latanoprost 0.005% (NCX 470 – latanoprost), in the time-matched IOP reduction from baseline (follow-up minus baseline) is ≤ 1.5 mmHg for all 6 time points (Week 2, 8 AM and 4 PM; Week 6, 8 AM and 4 PM; Month 3, 8 AM and 4 PM) and ≤ 1.0 at 4 or more of the 6 time points.

NCX 470 0.1% will be non-inferior to latanoprost if the null hypothesis (H_0) is rejected (i.e., the upper limit of the two-sided 95.1% confidence interval [CI] around the differences between the least squares [LS] mean of NCX 470 0.1% and the LS mean of the latanoprost group [NCX 470 – latanoprost] is ≤ 1.5 mmHg). If NCX 470 is non-inferior to latanoprost, then the superiority of the NCX 470 to latanoprost will be tested.

NCX 470 will be superior to latanoprost if the p-value for the testing treatment difference is ≤ 0.049 and the time-matched IOP LS mean difference in change from baseline at Week 2, Week 6, and Month 3 visits (NCX 470 – latanoprost) is < 0 at all 6 time points.

The 95.1% CI for the final primary efficacy analysis and the alpha of 0.049 for the superiority efficacy analysis, take into account the Week 2 interim analysis for the adaptive dose selection. As the definition for overall statistical non-inferiority requires demonstration of statistical non-inferiority at all 6 time points, no adjustment for multiplicity will be made at each time point.

Hierarchical fixed sequence testing will be made wherein superiority of NCX 470 0.1% QD to latanoprost 0.005% QD will be tested only if overall clinical non-inferiority is demonstrated. Statistical superiority will be concluded if statistical superiority is demonstrated at all 6 time points. As the definition for overall statistical superiority requires demonstration of statistical superiority at all 6 time points, no adjustment for multiplicity will be made at each time point. [redacted]

2.3 Primary Estimand

The primary comparisons in this trial will be between NCX 470 0.1% QD and latanoprost 0.005% QD at the 8 AM and 4 PM time points at the Week 2, Week 6, and Month 3 Visits in the Intent-to-Treat (ITT) population with intercurrent events handled as described in the following estimand:

- Population: subjects with Open-Angle Glaucoma or Ocular Hypertension defined through enrolment criteria

- Endpoint:
  - Reduction from baseline IOP (mm Hg) at the 8 AM and 4 PM time points at the Week 2, Week 6, and Month 3 Visits in the study eye
- Intercurrent event:
- Population-level summary:
  - The difference in the mean reduction from baseline IOP at the 8 AM and 4 PM time points at the Week 2, Week 6, and Month 3 Visits, between study eyes treated with NCX 470 0.1% QD and study eyes treated with latanoprost 0.005% QD.

Sensitivity analyses will be performed on observed data only and where

Additionally, tipping point analyses will be performed at each time point and visit for both non-inferiority and superiority.

Due to ongoing recruitment and enrollment during the SARS-CoV-2 pandemic,

[redacted]

3. Study Design and Procedures

3.1 General Study Design

This is a randomized, multi-regional, double-masked, parallel-group, active comparator-controlled, Phase 3 clinical trial with an adaptive dose selection. This study will be conducted in approximately 50 sites in the United States and in approximately 1 to 3 sites in China. [redacted] 670 will be randomized.

[redacted]

[redacted]

*Duration according to the subject's previous IOP-lowering treatment.

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, as shown in Table 1 of the protocol. Treatment-naïve subjects' Eligibility 1 Visit will be scheduled a minimum of [redacted] after the Screening Visit.

Successful washout and IOP-based eligibility for all subjects will be determined at the Eligibility 1 Visit and the Eligibility 2 Visit 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 measurements from the Eligibility 1 Visit and Eligibility 2 Visit. Subjects meeting eligibility requirements will be randomized and study medication will be dispensed at the end of the Eligibility 2 Visit.

During the initial adaptive design dose-ranging phase, at least 30 subjects were randomized in each arm in a 1:1:1 ratio to receive NCX 470 ophthalmic solution (0.065% or 0.1%), or latanoprost ophthalmic solution, 0.005% QD in the evening, one drop in each eye.

- NCX 470 ophthalmic solution, 0.065%
- NCX 470 ophthalmic solution, 0.1%
- Latanoprost ophthalmic solution, 0.005%

[redacted]

After this phase, subjects were randomized in a 1:1 ratio to receive the selected dose of the NCX 470 ophthalmic solution or latanoprost ophthalmic solution, 0.005% QD in the evening, one drop in each eye.

The study eye will be the eye [redacted]

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 Month 3/Exit Visit.

3.2 Study Visit Windows

Scheduled Visit	Planned Study Day	Visit Window
Screening*	N/A	[redacted]

Scheduled Visit	Planned Study Day	Visit Window
Eligibility 1 – 8 AM	Day -7 to -3	[redacted]
Eligibility 1 – 10 AM	Day -7 to -3	[redacted]
Eligibility 1 – 4 PM	Day -7 to -3	[redacted]
Eligibility 2 – 8 AM	Day 1**	[redacted]
Eligibility 2 – 10 AM	Day 1**	[redacted]
Eligibility 2 – 4 PM	Day 1**	[redacted]
Week 2 – 8 AM	Day 14	[redacted]
Week 2 – 10 AM	Day 14	[redacted]
Week 2 – 4 PM	Day 14	[redacted]
Week 6 – 8 AM	Day 42	[redacted]
Week 6 – 10 AM	Day 42	[redacted]
Week 6 – 4 PM	Day 42	[redacted]
Month 3 – 8 AM	Day 90	[redacted]
Month 3 – 10 AM	Day 90	[redacted]
Month 3 – 4 PM	Day 90	[redacted]

* Screening IOP is measured at one time point, 8 AM, 10 AM, or 4 PM.

** For the purposes of study day calculations Eligibility 2 is always [redacted], regardless of if the subject was treated on this day.

At the start of the ADSP some subjects were screened and completed parts of the eligibility visits, however due to the ADSP starting and putting the remaining eligibility activities on hold, these assessments needed to be collected a second time closer to the actual randomization that occurred after the ADSP hold on randomization ended. [redacted]

3.3 Schedule of Visits and Assessments

The schedule of visits and assessments is presented in Appendix 1.

3.4 Timing of the Interim Adaptive Dose Selection

[redacted]

[redacted]

3.5 Strategy for the Adaptive Dose Selection

[redacted]

[redacted]

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

At the Eligibility 2 Visit, utilizing the Interactive Response Technology (IRT) system, approximately 670 eligible subjects will be randomly assigned to one of two concentrations of NCX 470 or the active comparator latanoprost 0.005% solution in a masked fashion in a 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 the [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 system. 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]

5.1 Justification of Non-inferiority Margin

The results of the Phase 2 trial "Dolomites," NCX-470-17001 demonstrated that all tested concentrations of NCX 470 (0.021%, 0.042%, and 0.065%) QD met the primary efficacy endpoint of non-inferiority to latanoprost 0.005% QD for reduction from baseline in mean diurnal IOP at Day 28. In pre-specified secondary efficacy analyses, NCX 470 0.065% was superior to latanoprost for mean IOP reduction from baseline at all 3 time points (8 AM, 10 AM and 4 PM) on Day 28, with the difference reaching up to 1.4 mmHg. Mean IOP reduction from baseline at the 3 time points across Days 7, 14 and 28 ranged from 7.6 to 9.8 mmHg for NCX 470 0.065% compared with 6.3 to 8.8 mmHg for latanoprost.

6. Data Preparation

Study data will primarily be recorded on the electronic Case Report Forms (eCRFs) supplied by [redacted]

6.1 Data Preparation for the Interim Adaptive Dose Selection

Interim Adaptive Analysis was conducted when at least 30 subjects were randomized in each arm and completed the study through the Week 2 Visit. All assessments, AEs, protocol deviations and concomitant medications for the subjects through Week 2 were required to be entered by the site. Adverse event coding,

serious adverse event (SAE) EDC reconciliation, and key data points related to the following eCRF data was reviewed and cleaned by

- Intraocular Pressure
- Conjunctival Hyperemia
- Adverse Events/Serious Adverse Events
- End of Study (Subject discontinuation)
- Pachymetry
- Demographics
- Protocol Deviations

Upon confirmation that all required data was entered and there were no outstanding concerns in the data for the interim analysis, approval signature was obtained from . and from Nicox Ophthalmics, Inc. for to perform a data cut of the data in EDC. Approval for the masked EDC data cut and the unmasked cut required approval by at least 2 authorized representatives of Nicox, including the , or if one of these personnel were not available, other members of Nicox executive management may sign these approvals.

6.2 Input Data for Final Analysis

When all prerequisites for database lock have been met, including Sponsor approval, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study. Once the study has been unmasked, unmasked will be sent to . Any changes to the databases after data have been locked can only be made with the approval of the Sponsor in consultation with .

Final analysis will be carried out after the following have occurred:

- Database lock has occurred, including receipt of all final , with written authorization provided by appropriate and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

6.3 Output Data for Final Analysis

Data from EDC and will be transferred to and incorporated into standard formats following the Data will then be mapped to analysis datasets using the). Both will be used to create the subject listings, while all tables and figures will be based on the

will follow the and will be implemented using the and the .

[redacted] and will be implemented using [redacted] will be validated using [redacted]. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for [redacted]

7. Analysis Populations

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

7.1.1 Intent-To-Treat (ITT) 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.

7.1.2 Modified Intent-To-Treat (mITT) Populatio\

The modified ITT population is a subset of the ITT population excluding subjects with missing data due to COVID-19. Efficacy variables will be analyzed using the mITT population for sensitivity analyses. These analyses will be performed on an as-randomized basis.

7.1.3 Per Protocol (PP) Population

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 3-month treatment period. Demographics, baseline characteristics, and selected efficacy variables (refer to Table 2) will be analyzed using the PP population, in addition to the ITT and mITT populations. The PP analyses will be performed on an as-treated basis.

Two classifications of protocol deviations may be made. One for classifying GCP violations and a separate classification of protocol deviations for determining exclusions to the PP Population. Classifications may be discussed at the same time, however classifying GCP violations and classifications for exclusions from the PP Population will be independent of each other. Approval of protocol deviation classifications will be sought only for the exclusions from the PP Population.

7.2.3.1 PROTOCOL DEVIATIONS

All protocol deviations will be classified to determine the PP Population. Classifications will be determined programmatically in ADaM, where possible, or by the Medical Monitor and Sponsor in consultation from various members of the study team. The final PP population will be determined and approved by Nicox prior to database lock. The Medical Monitor, Sponsor, and lead biostatistician are required to approve all protocol deviation classifications prior to database lock and unmasking of treatment arms. A programmed protocol deviation listing and a listing of prohibited prior and concomitant medications will be provided to ensure thorough protocol deviation review.

[redacted]

7.1.4 Safety Population

The safety population will include all randomized subjects who received at least one dose of the study medication during the 3-month 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.

8. General Statistical Considerations

8.1 Unit of Analysis

The unit of analysis in this study will be the study eye for efficacy analyses [redacted]. The safety summaries will be performed for study and fellow eyes separately, as applicable.

Non-ocular assessments, including disposition, demographics, baseline characteristics, medical history, concomitant medications, study drug exposure, and AEs, will be summarized at the subject level. Ocular assessments will be summarized at the eye level.

8.2 IOP Unit of Analysis and Baseline IOP Definition

IOP will be measured at the 8 AM [redacted] for Screening and [redacted] at other visits), 10 AM [redacted] for Screening and [redacted] at other visits), and 4 PM [redacted] for Screening and [redacted] at other visits) time points at the Eligibility 1, Eligibility 2, Week 2, Week 6, and Month 3/Exit Visits. At Screening IOP is measured only once, at any one of the 3 time points.

[redacted]

Baseline time-matched IOP will be calculated as [redacted]

Baseline mean diurnal IOP will be calculated as:

[redacted]

The mean diurnal IOP values that are an average of 2 time points will be referred to as “mean diurnal IOP 2” and the values that are an average of 3 time points will be referred to as “mean diurnal IOP 3”.

For the changes from baseline (follow-up minus baseline), more extreme negative numbers indicate results in favor of the active treatment arm. However, the primary estimand will only be met if the upper bounds of the 95.1% CI around the change from baseline mean difference is less than or equal to 1.5 for all time points and less than or equal to 1.0 for 4 or more timepoints.

8.3 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.

8.4 Missing or Inconclusive Data Handling

8.4.1 Missing Efficacy Data Handling

Missing data for the primary efficacy analysis in the ITT population will be imputed using MI.

Due to ongoing recruitment and enrollment during the COVID-19 pandemic, two additional sensitivity analyses will be conducted.

8.4.2 Missing or Inconclusive Dates

Partial or missing dates, where complete dates are required to flag data as treatment-emergent or for prior and/or concomitant with treatment,

Partial/missing start date:

Partial/missing end date:

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

8.5 Data Analysis Conventions

All data analysis will be performed by after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using . 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 ID, visit (as applicable), and eye (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, SD, standard error (SE) (for efficacy analyses only), 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 SEs 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 0.049 ($\alpha = 0.049$), 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 is more than 1 assessment that falls into a scheduled visit window after 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 Month 3/Exit Visits for analyses. Event-based data (AEs, concomitant medications, etc.) will be listed by date and summarized regardless of visit types.

[redacted], this treatment group will not be presented on efficacy tables, but will be on the majority of dispositional, numbered 14.1, and safety tables numbered 14.3. An All NCX 470 group will be added as applicable.

9. 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, Physician decision, Sponsor or Institutional Review Board (IRB) decision, protocol violation, study termination by Sponsor, withdrawal by subject, [redacted] subject discontinued due to adaptive design, and other. COVID-19 relationship to reasons for study discontinuation and relationship to protocol deviations will be listed and summarized. Subject dispositions and registration information will also be listed.

The total number of screened subjects with the number and percentage of screen failure subjects will be summarized. The reasons for screen failure, both related to COVID-19 and unrelated, will be displayed with the percentages calculated using total number of screen failures as the denominator. Screen failed subjects, both related to COVID-19 and unrelated, with their reason for screen failure will be listed.

In addition, subject listings will be provided that include informed consent date, inclusion and exclusion criteria violations, and exclusions from the PP population. Details of the study randomization, including randomization date and time, randomized treatment and actual treatment, and stratification, will also be included within a subject listing.

The number and percentage of subjects with any deviation, classified as major or minor for PP Population exclusions and for GCP, will be summarized for each protocol deviation category by treatment group for all randomized subjects. The following protocol deviation categories will be summarized: [redacted] A subject listing will be provided that includes the date of the deviation, the deviation category, the deviation description, and the classification of whether the deviation was judged to be major or minor for PP Population exclusion and GCP violations in a masked review prior to database lock.

10. Demographics and Baseline Characteristics

The demographic variables collected in this study include age, age category (>=18 to <65, >=65, and >= 75 years), sex, race, ethnicity, and iris color measured at Eligibility 2 Visit. 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:

- Time-Matched Baseline IOP at 8 AM, 10 AM, and 4 PM
- Baseline mean diurnal IOP 2 (average of 8 AM, and 4 PM)
- Baseline mean diurnal IOP 3 (average of 8 AM, 10 AM, and 4 PM)
- Central corneal thickness
- Cup-to-disc ratio (horizontal)
- Cup-to-disc ratio (vertical)
- BCVA
- Conjunctival hyperemia per [redacted]
- PGA or NO-donating PGA at screening
- Number of IOP-lowering medications at screening
- EDC and IRT Stratification Categories

Baseline characteristics will be summarized by descriptive statistics and with a 95% confidence interval for continuous variables only.

Gonioscopy and manifest refraction assessments will be performed at Screening Visit and the results will be presented in subject data listings for all randomized subjects. Additionally, all demographic information will be presented on a subject data listing for all randomized subjects.

11. Medical History and Concomitant Medications

11.1 Medical History

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

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.

Ocular medical histories will be included on subject data listings sorted by treatment, subject, eye (both eyes, then study eye, then fellow eye) and ascending dates. Non-ocular medical histories will be included on subject data listings sorted by treatment, subject, and ascending dates. Summaries of SOCs and PTs will be sorted in descending frequency by the NCX 470 0.1% arm.

11.2 Prior and Concomitant Medications

All prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug; Global B3, March 2020) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical) and preferred name. If the 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 classification and preferred name of “Uncoded.”

Ocular 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 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 with an end date prior to the first dose of study drug. Concomitant medications will be defined as medications with an ongoing status or with an end date on/after the first dose of study drug.

Non-ocular prior and concomitant medications will be summarized by subject using the Safety population. Summaries of classification and preferred names will be sorted in descending frequency by the NCX 470 0.1% arm.

All prior and concomitant medications will be included on subject data listings sorted by eye (both eyes, then study eye, then fellow eye), prior and/or concomitant status, and ascending dates. IOP lowering medication will be indicated on listings and summarized on the baseline characteristics table for IOP lowering medications used prior to randomization.

A list of prohibited concomitant medications will be created to aid in the review of protocol deviations (see section 7.2.3.1 of this SAP). A Sponsor approved list of preferred names and/or [redacted] classifications will be used to determine prohibited concomitant medications.

12. Treatment Exposure of Study Drug and Compliance

The study medication is expected to be administered one drop in each eye by the subject or caregiver, at 8 PM [redacted] hours starting the evening of Eligibility 2 Visit to the evening prior to the subject's last study visit. Subject diaries are entered into EDC to capture treatment exposure and to calculate compliance. The Eligibility 2 Visit is the expected date of the first dose and should be used as Day 1 for all calculations.

Treatment Exposure will be defined as the number of days that the subject was exposed to study treatment as calculated using the formula:

Treatment Exposure (days) = Date of Last Dose – Date of First Dose + 1.

Expected Treatment Exposure will be defined as the number of days that the subject was supposed to be exposed to study treatment as calculated using the formula:

Expected Treatment Exposure (days) =
[(Date of Last Visit or Last Diary, whichever later) – Date of Eligibility 2 (Day 1) in EDC System], + 1 if later date is from the subjects' diary.

Compliance of study drug is calculated as:

100 * (Number of Days with Study Drug Taken) / (Expected Treatment Exposure).

In addition, compliance will also be summarized by treatment using the number and percentage of subjects in category of [redacted]

Descriptive summary statistics by treatment will be presented for treatment exposure, expected treatment exposure, and compliance in the ITT and safety population. Diary data will be listed for all randomized subjects. A listing will be produced with tallies of the number of days with study drug taken, number of days without study drug taken, treatment exposure, expected treatment exposure, and compliance for each subject.

13. Efficacy Analyses

All primary and secondary efficacy variables, along with the planned analysis methods for those variables, are given in Table 2. 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.

An analysis of covariance (ANCOVA) model with fixed-effect terms for baseline time-matched IOP and treatment as the main effect will be performed.

To check the appropriateness of the ANCOVA model, and additional ANCOVA will be run with the added treatment-by-baseline interaction term added to the model.

The LS mean of NCX 470 0.1% and latanoprost 0.005% will be obtained from the ANCOVA model with fixed-effect terms for baseline time-matched IOP and treatment. The NCX 470 0.1% group will be compared with the latanoprost 0.005% group by computing a two-sided 95.1% CI around the differences between the LS mean of the NCX 470 0.1% group and the LS mean of the latanoprost group. The differences between treatment groups will be calculated as NCX 470 0.1% minus latanoprost 0.005%. For each comparison, the two-sided p-values will also be presented.

[redacted]

All efficacy variables will be summarized by treatment descriptively.

[redacted]

Table 2. Summary of Efficacy Variables and Analysis Methods

Efficacy Variable	t-test[1]	ANCOVA[2]	Analysis Population	Missing Data Imputation
[redacted]				

[1] One-sample t-test will be used to test if the change from baseline is different from zero and a two-sample t-test will be used to compare the mean baseline IOPs of each arm.

[2] The primary ANCOVA model will have baseline as a covariate and treatment as the main effect. A second ANCOVA model will test the baseline-by-treatment interaction term.

[redacted]

13.1 Primary Analysis

The primary efficacy variable is the change from baseline in time-matched IOP of the 8 AM and 4 PM time points to Week 2, Week 6, and Month 3 visits, calculated as time-matched IOP at follow-up visit minus baseline IOP. Baseline is based on Eligibility 1 and Eligibility 2 Visit measurements (see Section 8.3). Listings with the individual measurements and the "base" unit for both eyes will be produced, and the mean diurnal IOP average of 2 (8 AM and 4 PM) and 3 (8 AM, 10 AM, and 4 PM) time points will be on a separate listing. The primary analysis will be based on the study eyes for the ITT population using MI to impute missing data.

The primary efficacy assessment is the non-inferiority analysis of the difference in the treatment effect between each NCX 470 0.1% and latanoprost 0.005% in change from baseline in time-matched IOP to the follow-up visits (Week 2, Week 6, and Month 3), based on study eyes for the ITT population using MI to impute missing data.

An analysis of covariance (ANCOVA) model with fixed-effect terms for baseline time-matched IOP and treatment as the main effect will be performed.

The LS mean of the NCX 470 0.1% treatment groups and latanoprost will be obtained from the ANCOVA model. NCX 470 0.1% group will be compared with the latanoprost group by computing a two-sided 95.1% CI around the differences between the LS mean of the NCX 470 0.1% treatment groups and the LS mean of the latanoprost group. The differences between treatment groups will be calculated as NCX 470 0.1% dose minus latanoprost 0.005% dose. For each comparison, the two-sided p-values will also be presented.

Additionally, the equality of baseline time-matched IOP between NCX 470 0.1% and latanoprost 0.005% will be tested using a two-sample t-test. For the change from baseline in time-matched IOP, one-sample t-tests will be performed for all treatment groups to test whether the change from baseline is significantly different from zero within the treatment group.

[redacted]

[redacted]

The following example line of code will be added to the `proc mi` for the control-based MCMC imputations:

[redacted]

[redacted]

13.2 Sensitivity Analyses

To assess the robustness of the primary analysis results, sensitivity analyses will be performed based on the PP population with observed data and MI similar to the primary endpoint. Sensitivity analyses will also be performed on the ITT population using observed data and a tipping point analysis. Also, for the ITT population using [redacted]. COVID-19 related missingness with be investigated with similar randomized treatment-based and control-based imputation methods as the primary analysis in the ITT population. [redacted]

For the sensitivity analyses, the statistical analysis method will be similar to the primary analysis as described in Section 13.1.

13.3 Secondary Analyses

Secondary efficacy variables include:

[redacted]

The statistical analysis method will be similar to the primary analysis as described in Section 13.1, but imputations and 1-sample t-tests will not be performed to test whether the change from baseline is significantly different from zero within any treatment group. Secondary analyses will be conducted in the ITT and PP populations with observed data only.

13.4 Exploratory Analyses

Exploratory efficacy variables include:

[redacted]

[redacted]

For numbers and proportion outputs, Fisher's exact test (two-sided p-values) will be used to test the pair-wise differences between the NCX 470 0.1% and latanoprost at each visit.

For (6), the statistical analysis methods will utilize a one-sample t-test and ANCOVA with treatment, and baseline as the only covariates.

For (7), the statistical analysis methods will utilize a one-sample t-test and ANCOVA with treatment, and baseline as the only covariates for the analysis of treatment naïve subjects, and for subjects on IOP-lowering medication at Screening Visit. Other subgroup analyses enumerated in (7) will be assessed with descriptive summary statistics only.

For (8), descriptive summary statistics will be presented.

13.5 Subgroup Analyses

Mean diurnal IOP [redacted]) and time-matched IOP, change from baseline and percent change from baseline in the study eyes using observed data for the ITT population will be analyzed by stratification group [redacted]). If any stratification factor is different between the IRT and EDC systems the factor entered by site personnel in EDC on Eligibility 2 (Day 1) will be used. Corrections made to EDC after Day 1 affecting the stratification will be mentioned on table footnotes only if they are used in analyses.

Similarly mean diurnal IOP ([redacted]) and time-matched IOP, change from baseline in the study eyes using observed data for the ITT population will be analyzed by race group [redacted]

For the subgroup analyses, the statistical analysis methods will utilize a one-sample t-test and ANCOVA with treatment, and baseline as the only covariates. Additionally, the equality of baseline time-matched IOP between NCX 470 0.1% and latanoprost 0.005% will be tested using a two-sample t-test.

14. Safety Analyses

All safety summaries will be based on the safety population. All safety data will be presented on subject listings in the safety population.

14.1 Adverse Events

AEs will be coded using MedDRA, [redacted]

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, non-ocular TEAE, serious ocular TEAE, serious non-ocular TEAE, serious ocular TEAE related to the study drug, serious non-ocular TEAE related to the study drug, ocular TEAEs by maximum severity, non-ocular TEAEs by maximum severity, ocular TEAEs by strongest relationship to study drug, non-ocular TEAEs by strongest relationship to study drug, ocular TEAEs leading to study drug withdrawal, 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 leading to study drug withdrawal
- Non-ocular TEAEs leading to study drug withdrawal
- Ocular TEAEs by maximal severity
- Non-ocular TEAEs by maximal severity
- Ocular TEAEs by strongest relationship to study drug
- Non-ocular TEAEs by strongest relationship to study drug

All TEAEs, all serious TEAEs, and TEAEs leading to study drug withdrawal will be presented in subject data listings. Listings will be sorted by subject, eye (both eyes, then study eye, then fellow eye events), then non-ocular events, by ascending dates. Tables will be sorted by the descending frequencies of the SOC and PTs in the all NCX 470 group.

14.2 Best-Corrected Visual Acuity

Best-corrected visual acuity (BCVA) will be assessed at the Screening Visit, and at the 8 AM time point during the Eligibility 1, Eligibility 2, Week 2, Week 6, and Month 3/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.

14.3 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 Visit, and at the 8 AM time point during the Eligibility 1, Eligibility 2, Week 2, Week 6, and Month 3/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]

14.4 Anterior Chamber

Anterior chamber cells and flare will be assessed in both eyes at the Screening Visit, and at the 8 AM time point during the Eligibility 1, Eligibility 2, Week 2, Week 6, and Month 3/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]

14.5 Conjunctival Hyperemia

Conjunctival hyperemia, measured by the [redacted] will be assessed in both eyes at the Screening Visit, and at the 8 AM time point during the Eligibility 1, Eligibility 2, Week 2, Week 6, and Month 3/Exit visits.

The redness grades [redacted] 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]

14.6 Dilated Ophthalmoscopy Examination

A dilated ophthalmoscopy examination of the vitreous, retina, macula, choroid, optic nerve, and cup-to-disc will be performed in both eyes at the Screening Visit and the 4 PM time point at the Month 3/Exit Visit. 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.

In addition, cup-to-disc ratios (horizontal and vertical) will be assessed in both eyes at the Screening Visit and the 4 PM time point at the Month 3/Exit Visit. 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.

14.7 Pachymetry

Pachymetry assessment will be performed at the Screening Visit and the 4 PM time point at the Eligibility 2, Week 2 (for subjects participating in the adaptive phase only), and Month 3/Exit Visits for both eyes. There will be readings of central corneal thickness in each eye at each visit. The will be used as central corneal thickness value for summaries.

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

14.8 Intraocular Pressure

IOP measurements are taken according to Section 8.3 of this SAP and the “base” unit is used for the safety analyses. Baseline will be the time-matched baseline which is an average of the Eligibility 1 and Eligibility 2 “base” measurements.

The number and percentage of subjects with a mmHg increase from baseline, mmHg increase from baseline, and increase from baseline at any point after randomization in study eye, fellow eye, or either eye by visit and time point, and at any post-baseline time points of the study will be summarized by treatment.

14.9 Pupil Size

Pupil size or pupil diameter in mm will be assessed at the Screening Visit, and at 8 AM time point during the Eligibility 1, Eligibility 2, Week 2, Week 6, and Month 3/Exit visits. Pupil size (mm) will be summarized by treatment at each visit using continuous summaries, including change from baseline, for both the study eyes and the fellow eyes.

14.10 Visual Field

The visual field examination will be completed at the Screening Visit and at the 8 AM time point at the Month 3/Exit Visit. The results ( ]) 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. Visual field reliability ( ) will also be summarized with the number of subjects and percentages with “Yes” or “No.”

[redacted]

14.11 Iris Color

Iris Color will be assessed for both eyes at Screening, and at the 8 AM time point during the Eligibility 2 and Month 3/Exit visits. The Eligibility 2 assessment will be listed and summarized on the demographics outputs while the additional assessments of iris color will be on a separate listing and table, noting any changes from Eligibility 2 on the listing.

14.12 Urine Pregnancy Test

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

15. Interim Analyses

A planned unmasked interim adaptive analysis was performed [redacted]

The adaptive dose selection occurred per the interim analysis SAP, resulting in the following events:

[redacted]

No other interim analyses are planned.

[redacted]

15.1 Determination of the Alpha Spending Function

[redacted]

16. Changes from Protocol-Stated Analyses

[redacted]

Analyses related to COVID-19 have been added as the study enrolled subjects during the COVID-19 pandemic. Additionally a mITT population has been added to exclude subjects who have missing data related to COVID-19.

Multiple exploratory and subgroup analyses have been added to support the varying interests of the Sponsor. Statistical methods are explained in sections 13.4 and 13.5.

[redacted]

17. Changes from Statistical Analysis Plan

This version 2.0 of the Full SAP is the initial version for the final analysis. Changes will be recorded on any future versions of the Full SAP if they occur beyond version 2.0.

18. References

1. 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)
2. 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)

19. List of Tables and Listings

19.1 List of Tables

Topline tables are bolded and in italics.

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

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Table Number	Title	Population
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20. Appendix 1 Schedule of Visits and Assessments

	Screening Visit	Eligibility 1 Visit Day [redacted]			Eligibility 2 Visit Day [redacted]			Week 2 Visit Day 14 [redacted])			Week 6 Visit Day 42 [redacted])			Month 3/ Exit Visit Day 90 [redacted])		
Time		**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/Changes in MH/OH	X	X			X			X			X			X		
Concomitant medications[a]	X	X			X			X			X			X		
[redacted]																
Adverse events[g]	X	X			X			X			X			X		
Randomization (IRT/EDC)[h]							X									
Dispense study medication[i]							X						X			
Collect study medication											X			X		
Dispense/collect subject diary[j]							X	X			X			X		
Study exit (IRT/EDC)														X