NCT 05591755

STATISTICS & DATA CORPORATION

STATISTICAL ANALYSIS PLAN

A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled Evaluation of the Onset and Duration of Action of the Combination Drug Product Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution Compared to its Components and Vehicle in an Allergen BioCube® (ABC®) Clinical Trial in Subjects with Seasonal Allergic Conjunctivitis

Sponsor: Bausch & Lomb, Incorporated.
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Protocol Number: 910

Date: 29Sep2023
Version: 2.0

Table of Contents

List of Abbreviations

Abbreviation	Definition
ABC	Allergen BioCube
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
CC	With Correction
Combo	Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution
CS	Clinically Significant
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent to Treat
logMAR	Logarithm of the Minimum Angle of Resolution
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
NCS	Not Clinically Significant
OD	*Oculus dexter* (Right Eye)
OS	*Oculus sinister* (Left Eye)
PEFR	Peak Expiratory Flow Rate
PNIF	Peak Nasal Inspiratory Flow
PP	Per Protocol
PT	Preferred Term
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Without Correction
SD	Standard Deviation
SDC	Statistics & Data Corporation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Treatment-Emergent Serious Adverse Event
TNSS	Total Nasal Symptom Score
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol 910, Amendment 2 dated 31Jul2023.

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.

2. Study Objective and Study Parameters

2.1 Study Objective

The primary objective is to evaluate the efficacy of Brimonidine tartrate 0.025%/Ketotifen fumarate 0.035% ophthalmic solution (Combo) compared to its individual components and vehicle in a population of subjects with seasonal allergic conjunctivitis.

2.2 Study Parameters

2.2.1 Efficacy Measures and Endpoints

2.2.1.1 Primary Efficacy Measures and Endpoints

- Ocular itching score (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned investigational product (IP) at Visit 2 ([redacted]
- Ocular redness score (average score of the subject's two eyes) evaluated by the investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]

2.2.1.2 Secondary Efficacy Measures and Endpoints

- Tearing (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]

- Lid swelling (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Chemosis (average score of the subject's two eyes) evaluated by the investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]

2.2.1.3 Exploratory Efficacy Measures and Endpoints

- Nasal itching (nasal pruritus) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Rhinorrhea evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Nasal congestion evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Sneezing evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Total Nasal Symptom Scores (TNSS) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 (composite score of Nasal Itching, Nasal Congestion, Rhinorrhea and Sneezing, sum of the four component scores)
- Peak Nasal Inspiratory Flow (PNIF) measured pre-Allergen BioCube® (ABC) exposure, and 60, 90, and 480 minutes post-instillation of assigned IP at Visit 2 (measured by means of a peak flow meter in L/min)

2.2.2 Safety Measures

- Adverse Events (AEs; reported, elicited and observed)
- Best-Corrected Visual Acuity (BCVA) at distance utilizing an early treatment diabetic retinopathy study (ETDRS) chart
- Slit-lamp Biomicroscopy
- Intraocular Pressure (IOP)
- Dilated Fundoscopy
- Vital signs
- Peak Expiratory Flow Rate (PEFR)

2.3 Statistical Hypotheses and Adjustments for Multiplicity

Statistical success will be achieved if all of the following four conditions are met at Visit 2:

1. The Combo is superior in ocular itching to Vehicle (evaluated by the subject)

2. The Combo is superior in ocular redness to Vehicle (evaluated by the investigator)
3. The Combo is superior in ocular itching to brimonidine tartrate ophthalmic solution, 0.025% (evaluated by the subject)
4. The Combo is superior in ocular redness to ketotifen fumarate ophthalmic solution, 0.035% (evaluated by the investigator)

Hypothesis testing will be split into two groups. Hypotheses associated with the first three time points will constitute the first group and hypotheses associated with the latter three time points will constitute the second group.

Testing of the first three time points will be performed first. If the treatment effect is not statistically significant (one-sided $\alpha = 0.0083 = 0.025/3$ to account for the three time points) at any of the three time points, then the condition is not met.

If the treatment effect is statistically significant for at least one of the first three timepoints, then the second group of hypotheses is tested.

If the treatment effect was statistically significant for exactly one of the three comparisons in the first group, this leaves 0.0083 alpha unused and all three treatment effects in the second group of hypotheses must be statistically significant at the unused one-sided alpha=0.0083/3=0.0028 in order for this condition to be met..

If the treatment effect was statistically significant for exactly two of the three comparisons in the first group, this leaves 0.0167 alpha unused and at least two treatment effects in the second group of hypotheses must be statistically significant at the adjusted unused one-sided alpha=0.0167/3=0.0056 in order for this condition to be met..

If the treatment effect was statistically significant for all three comparisons in the first group, this leaves 0.025 alpha unused, and at least one treatment effect in the second group of hypotheses must be statistically significant at the adjusted unused one-sided alpha=0.025/3=0.0083 in order for this condition to be met.

2.3.1 Hypotheses

Superiority Tests

For each primary endpoint (ocular itching and ocular redness) at each of the six evaluation time points post-instillation of IP, superiority hypotheses will be tested comparing the Combo to a comparator ketotifen fumarate 0.035% (for ocular redness), brimonidine tartrate 0.025% (for ocular itching), or Vehicle (for ocular redness and ocular itching). The null hypothesis (H_0) is that the mean score for the subjects in the Combo test group (μ_T) is greater than or equal to the mean score for the subjects in the comparator group (μ_C). The alternative hypothesis (H_1) is that the mean score for the subjects in the test group is less than the mean score for the subjects in the comparator group.

$$H_0: \mu_T \geq \mu_C$$

$$H_1: \mu_T < \mu_C$$

2.3.2 Multiplicity

Hypothesis testing will be split into two groups. Hypotheses associated with the first three time points will constitute the first group, and hypotheses associated with the latter three time points will constitute the second group.

Testing of the first three time points will be performed first. If the treatment effect is not statistically significant (one-sided α=0.0083=0.025/3 to account for the three time points) at any of the three time points, then the condition is not met.

If the treatment effect is statistically significant for at least one of the first three time points, then the second group of hypotheses is tested.

The overall Type I error rate including the primary and secondary efficacy analyses will be controlled by a hierarchical testing structure. Specifically, statistical inference for the secondary efficacy analyses will only be performed if the primary analyses are successful, after which inference for the secondary efficacy endpoints will be performed in a hierarchical manner in the order of the secondary endpoints from Section 2.2.1.2.

3. Study Design and Procedures

3.1 General Study Design

This is a multi-center, double-masked, randomized, parallel-group, vehicle-controlled study.

The study will consist of 2 study visits: a screening visit (Visit 1) to verify subjects are eligible to participate and a qualification/treatment visit to evaluate the onset of action and potential for an 8 hour duration of effectiveness for the brimonidine tartrate/ ketotifen fumarate combo drug product compared to its individual components and vehicle.

At Visit 1, subjects will sign the informed consent form (ICF) and an allergic skin test will be performed, if required. At Visit 2, subjects will undergo 90 minutes of exposure to pollen in the ABC®. Subjects who have a sufficient ocular allergy score (defined as a bilateral score of ≥2 in both ocular itching and ocular redness) at the 90 minute time point will be randomized 1:1:1:1 to receive one of the following, bilaterally, at Visit 2:

- Combo (Brimonidine tartrate 0.025%/Ketotifen fumarate 0.035% ophthalmic solution)
- Ketotifen fumarate ophthalmic solution, 0.035%
- Brimonidine tartrate ophthalmic solution, 0.025%
- Vehicle ophthalmic solution

Treatment will begin at Visit 2 following the 90 minute time point. Following instillation of investigational product, randomized subjects will remain exposed to pollen in the ABC® for an additional 8 hours. Assessments will be conducted at the designated time points.

If subjects do not have a sufficient ocular allergy score at the 90 minute time point and also have a positive skin test reaction to both ragweed and timothy grass, they may be rescreened for Visit 2 using the alternate pollen. In the event that subjects do not receive a full 90 minutes of pollen exposure (e.g., early exit from the ABC®, mechanical issue with pollen distribution), subjects may also be eligible for re-screening. Re-screening should take place at least one week following the initial Visit 2 and should be within the specified study visit windows.

Table 1. Schedule of Visits and Assessments

Visit	Visit 1	Visit 2
Day	-45 to -1	1
PROCEDURE		
General Assessments		
Informed Consent & HIPAA	X	
Demographic Data	X	
Medical & Medication History	X	
Update Medical & Medication History		X
Allergic Skin Test	X	
Urine Pregnancy Test		X
Ocular & Nasal Allergic Signs & Symptoms Assessment		X[1]
Review Incl./Excl. criteria	X	X
Enrollment/Randomization		X
AE Assessment	X	X[2]
TEAE Assessment		X[3]
Allergen Exposure in ABC®		
90 Minute Qualification Exposure		X
8 Hour Post-Treatment Exposure		X
Visual/Systems Exams		
Visual Acuity Utilizing an ETDRS chart	X	X[4]
Slit Lamp Biomicroscopy	X	X[4]
Intraocular Pressure	X	X
Dilated Fundoscopy	X	X
Peak Nasal Inspiratory Flow (PNIF)		X[1]
Peak Expiratory Flow Rate (PEFR)	X	X[1]
Vital Signs (pulse and blood pressure)	X	X
Investigational Product		
In-Office IP Instillation		X
Exit from Clinical Trial		
Study Exit		X

[1] Performed pre- and post-IP instillation during ABC® exposure.
[2] Prior to first dose of IP.
[3] Following first dose of IP.
[4] Performed pre- and post-ABC exposure.

4. Treatment Plan

4.1 Methods of Assigning Subjects to Treatment Groups

All subjects screened for the study who sign an ICF will be assigned a screening number that will be entered in the Screening and Enrollment Log. The screening number will consist of three (3) digits, starting with 001.

Once a subject meets all qualification criteria at Visit 2, he/she will be randomized to Combo, ketotifen fumarate ophthalmic solution 0.035%, brimonidine tartrate ophthalmic solution 0.025%, or Vehicle in a 1:1:1:1 ratio. Each subject who is randomized will be assigned a unique Randomization number in the Randomization and Trial Supply Management (RTSM). Randomization numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted. Randomization numbers will be 5 digits and will be created in the RTSM. Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across the RTSM treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

5. Sample Size and Power Considerations

A sample size of 50 subjects in each treatment group yields 98% power to demonstrate each of the following:

- The Combo is superior in ocular itching to Vehicle (evaluated by the subject)
- The Combo is superior in ocular redness to Vehicle (evaluated by the investigator)
- The Combo is superior in ocular itching to brimonidine tartrate ophthalmic solution, 0.025% (evaluated by the subject)
- The Combo is superior in ocular redness to ketotifen fumarate ophthalmic solution, 0.035% (evaluated by the investigator)

Assuming a one-sided $\alpha = 0.0083$, a true mean difference of 0.65 units and a common standard deviation of 1.0 units at each time point for each measure.

To allow for 10% dropouts, 56 subjects will be randomized in each of the treatment groups.

6. General Statistical Considerations

All data analysis will be performed by Statistics & Data Corporation (SDC) after the study is completed and the database has been locked. Analysis datasets will be created using data obtained from electronic data capture (EDC) and external data if applicable. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Outputs will be provided in portable document format (PDF) for tables, listings, and figures using landscape format. Tables will also be provided in rich text format (RTF).

All study data will be listed by subject, treatment, visit, and parameter, as applicable, based on all randomized subjects, unless otherwise specified. Listings will be sorted by subject number, visit date, time, and parameter, as applicable.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, SD, 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 more decimal place than reported in the raw values. Standard deviations will be presented to two more 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 one-sided with a significance level of 0.05 ($\alpha = 0.05$), unless otherwise specified. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; and p-values greater than 0.9999 will be presented as ">0.9999."

7. Analysis Populations

7.1 Intent to Treat Set

The Intent to Treat (ITT) Set will include all randomized subjects who are instilled with study drug. The ITT Set will be analyzed as randomized.

7.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who are instilled with study drug and have at least one post-instillation of study drug assessment of both primary endpoints. The FAS will be analyzed as randomized.

7.3 Per Protocol Set

The Per Protocol (PP) Set will consist of FAS subjects with no protocol violations considered to affect the evaluability of efficacy, as determined through masked review of deviations prior to unmasking. The PP Set will be analyzed as treated.

7.4 Safety Set

The Safety Set will include all subjects who receive any amount of study drug. The Safety Set will be analyzed as treated.

8. General Statistical Considerations

8.1 Unit of Analysis

For efficacy and non-ocular safety analyses, the unit of analysis will be the subject. In the cases where assessments are recorded for each eye, the average of the eyes will be used. Adverse events will also be summarized at the subject level; if an AE occurs in either or both eyes, the subject will be counted as having the AE. For other ocular safety analyses, the unit of analysis will be each eye (with summaries showing results for the right eye [OD] and the left eye [OS] separately).

8.2 Missing Efficacy Data Imputations

The primary efficacy analysis will be conducted with intercurrent events handled in the following manners:

1. Withdrawal due to lack of efficacy or AEs (assumed to be missing not at random [MNAR]): missing data will be imputed employing single imputation using worst observation carried forward (hypothetical strategy)
2. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs (assumed to be missing at random [MAR]): missing data will be imputed employing multiple imputation using randomized, treatment-based Markov chain Monte Carlo (MCMC) methodology to impute non-monotone missing and using randomized, treatment-based regression methodology to impute monotone missing (hypothetical strategy).

Additional sensitivity analyses will be performed assuming all missing values due to withdrawal of any kind imputed employing:

- Single imputation using worst observation carried forward (Subject-evaluated symptoms and investigator-evaluated signs (efficacy measures) will only be assessed at Visit 2. A missing post-instillation value will be imputed using the worst value (largest value) from previous post-instillation timepoints. If all post-instillation values are missing, all the missing values will be imputed using the pre-instillation value.
- Multiple imputation using randomized, treatment-based Markov chain Monte Carlo (MCMC) methodology to impute non-monotone missing and using randomized treatment-based regression methodology to impute monotone missing.

8.3 Other Missing or Inconclusive Data Handling

In general, there will be no other imputation of missing data other than for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of the first dose date of study drug, in which case missing day will be imputed as the first dose day of study drug.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of the first dose date of study drug, in which case missing day and month will be imputed as the day and month of the first dose of study drug.
- Completely missing dates will be imputed as the first dose date of study drug unless the end date is on or before the first dose date, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month.

- Dates with both day and month missing will be imputed as 31 Dec.
- If the ongoing flag is missing or "Yes" then the date will not be imputed.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

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).

COVID-19-related missing data or visits will not be imputed for summaries and analyses but will be reported as protocol deviations and recorded in protocol deviation log.

8.4 Scheduled/Unscheduled Visits

Only scheduled visits will be used for the visit-related summaries and analyses, unless specified otherwise. Unscheduled visits will be presented in data listings.

8.5 Definition of Baseline

Baseline is defined as last non-missing assessment prior to the first dose of study drug. Change from baseline will be calculated as Post-baseline Visit – Baseline Visit.

9. Disposition of Subjects

Summary for subject disposition by treatment group and overall will include:

- Number of screen failures (from all subjects)
- Number of randomized subjects
- Number and percentage of subjects for each of the study populations (ITT Set, FAS, PP Set, and Safety Set)
- Number and percentage of subjects who completed the study.
- Number and percentage of subjects discontinued from the study and the reasons for discontinuation.
- Number and percentage of subjects who discontinued for reasons related to COVID-19

Percentages for the subject disposition summary are based on number of randomized subjects.

Subject listings will be provided that include disposition, informed consent date, inclusion and exclusion criteria, and exclusions from the analysis sets and reason for exclusion from population. Details of the study randomization, including randomization date and time, randomized and actual treatment, dispensed kit number, and reason for unmasking (if applicable) will also be included within a subject listing.

10. Protocol Deviations

The number and percentage of subjects with any deviation, important deviations, not-important deviations, and COVID-19 related protocol deviations will be summarized by treatment group and overall for the ITT

Set. The number and percentage of subjects with any deviation in each deviation category (01 - Informed Consent, 02 - Inclusion / Exclusion, etc.) will also be summarized).

A subject listing will be provided for protocol deviations that includes the visit at which the deviation occurred, the deviation code, the deviation description, whether the deviation was related to COVID-19,and the classification of the deviation as important or not-important.

11. Demographics and Baseline Characteristics

Demographics and baseline characteristics will include sex, childbearing potential (yes, no), age in years at signing of ICF, age group (<65 years, ≥65 years), race, ethnicity, iris color for OD and OS, subject taking any medications that require a washout (yes, no), and washout time period (3 days, 7 days, 14 days, 45 days, and 60 days). Subjects who record more than one race will be grouped into the single category denoted as Multi-racial. Demographic data will be summarized by treatment group and overall for all subjects in the ITT Set.

Allergic skin test results (Positive, Negative, Not Assessed/Not Done) at Screening will be summarized by treatment group.

Subject listings that includes all demographic data and allergic skin test data will be provided.

12. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. Ocular and non-ocular medical history will be summarized at the subject level separately by system organ class (SOC), preferred term (PT), and treatment group for the ITT Set. If a subject has more than one SOC or PT within an SOC, they will only be counted once for that SOC or PT

Medical history data will be presented in a subject listing.

13. Prior or Concomitant Medications

Prior or Medications will be coded using World Health Organization Drug Dictionary (WHODrug; Global B3, March 2022). Concomitant medications will be defined as medications used on or after the first dose date of study drug. Prior medications will be defined as medications used prior to the first dose date of study drug, including the medications starting prior to the first dose date of study drug and continuing simultaneously with the study treatment. Ocular and non-ocular prior and concomitant medications used at the subject level will be summarized separately by the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification), preferred name, and treatment group for the Safety Set. 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 presented as the preferred name.

Reported and coded terms (ATC class and preferred name) for ocular and non-ocular medications will be presented in a subject listing.

14. Statistical Analyses

14.1 Analyses of Primary Efficacy Endpoints

The primary efficacy endpoints are:

- Ocular itching score (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned investigator product (IP) at Visit 2 ([redacted]
- Ocular redness score (average score of the subject's two eyes) evaluated by the investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]

Statistical success will be achieved if all of the following conditions are met at Visit 2:

- The Combo is superior in ocular itching to Vehicle (evaluated by the subject)
- The Combo is superior in ocular redness to Vehicle (evaluated by the investigator)
- The Combo is superior in ocular itching to brimonidine tartrate ophthalmic solution, 0.025% (evaluated by the subject)
- The Combo is superior in ocular redness to ketotifen fumarate ophthalmic solution, 0.035% (evaluated by the investigator).

Each primary endpoint will be summarized at baseline and for each post-instillation of study drug time point at Visit 2 by treatment group using continuous summary statistics for the ITT Set.

14.1.1 Primary Analysis

The primary efficacy analysis of primary efficacy endpoints will be conducted with intercurrent events handled in the following manners:

1. Withdrawal due to lack of efficacy or AEs (assumed to be MNAR): missing data will be imputed employing single imputation using worst observation carried forward (hypothetical strategy)
2. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs (assumed to be MAR): missing data will be imputed employing multiple imputation using randomized, treatment-based MCMC methodology to impute non-monotone missing and using randomized, treatment-based regression methodology to impute monotone missing (hypothetical strategy).

Treatment effects will be estimated and the statistical hypotheses will be tested using an analysis of covariance (ANCOVA) model with the efficacy variable as the dependent variable, treatment as a factor, and

corresponding baseline score as a covariate. Estimated least square mean differences between treatment groups and associated 95% CI, and overall p-values will provided.

14.1.2 Sensitivity Analyses

The sensitivity analyses will include the imputation models, analysis methods, and analysis sets as stated on Table 2.

Table 2. Sensitivity Analyses Methods

	Missing Values Imputation	Analysis Method(s)	Analysis Set(s)
1	The same as the primary analysis	Two-sample t-tests	ITT Set
2	The same as the primary analysis	Two-sample t-tests, ANCOVA	PP Set
3	Multiple imputation using a randomized, treatment-based MCMC for non-monotone missing and a randomized, treatment-based regression methodology for monotone missing	Two-sample t-tests, ANCOVA	ITT Set
4	Worst observation carried forward	Two-sample t-tests, ANCOVA	ITT Set
5	Observed values only	Two-sample t-tests, ANCOVA	ITT Set, FAS, PP Set

Note: ANCOVA model has the efficacy variable as the dependent variable, treatment as a factor, and corresponding baseline score as a covariate.

Refer to Section 17 for SAS codes for multiple imputations.

14.1.3 Subgroup Analyses

Primary efficacy endpoints using observed values only based on the ITT Set will be analyzed in the same manner as the Sensitivity Analysis Method #5 (Table 2) for subgroups of age (<65 vs ≥65 years), sex (male vs female), and race (white vs others).

14.2 Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Tearing (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]
- Lid swelling (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]

- Chemosis (average score of the subject's two eyes) evaluated by the investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]

Statistical inference for the secondary endpoints will only be performed if the primary efficacy analyses are considered successful. Secondary endpoints will be evaluated hierarchically in the order presented above. Success for each secondary endpoint will follow the same criteria as the primary endpoint. Primary analysis for the secondary efficacy endpoints will be performed in the same manner as the primary analysis for primary efficacy endpoints. Sensitivity analyses for the secondary endpoints will be performed in the same manner as the sensitivity analyses for the primary endpoints (Table 2).

Secondary efficacy endpoints using observed values only based on the ITT Set will be analyzed in the same manner as the Sensitivity Analysis Method #5 (Table 2) for subgroup of age (<65 vs ≥65 years), sex (male vs female), and race (white vs non-white).

14.3 Analyses of Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- Nasal itching (nasal pruritus) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]
- Rhinorrhea evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]
- Nasal congestion evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]
- Sneezing evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]
- Total nasal symptom scores (TNSS) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 (composite score of Nasal Itching, Nasal Congestion, Rhinorrhea and Sneezing)
- Peak nasal inspiratory flow (PNIF) measured pre-ABC® exposure to 8 hours post-instillation of assigned IP at Visit 2 (measured by means of a peak flow meter in L/min)

Only observed values will be used for the analyses of the exploratory efficacy endpoints. The exploratory efficacy endpoints will be summarized descriptively at baseline and each post-baseline time points by treatment group. The exploratory efficacy endpoints will be analyzed using two-sample t-tests assuming equal variance and a ANCOVA model with the efficacy variable as the dependent variable, treatment as a factor, and baseline score as a covariate. P-values will provided. The analyses will be based on the ITT Set.

14.4 Analyses of Safety Measures

14.4.1 Adverse Events

AEs will be coded using the MedDRA Version 25.0.

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset dates on or after the first dose date of study drug. Incidences and percentages of TEAEs will be summarized at the subject level by SOC and PT for all TEAEs, treatment-related TEAEs, treatment-emergent serious adverse events (TE-SAEs), and TEAEs causing premature study drug withdrawal by treatment group. Similar summaries will be presented for all TEAEs by maximal severity. Separate summaries will be performed for ocular and non-ocular AEs. The analyses will be based on the Safety Set.

AEs, serious adverse events (SAEs), and AEs causing premature study drug withdrawal will be presented separately in subject listings.

14.4.2 BCVA Utilizing an ETDRS Chart

Actual values for BCVA in logarithm of the minimum angle of resolution (logMAR) will be summarized for OD and OS separately by treatment group for Visit 1, and Visit 2 before qualification ABC and post-treatment ABC. Change from baseline to Visit 2 post-treatment ABC will also be summarized. In addition, correction used (without correction [SC], with correction [CC]) and pinhole used (Yes, No) will also be summarized using number of subjects and percentages. The analyses will be based on the Safety Set.

14.4.3 Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopic results (normal, abnormal not clinically significant [NCS], abnormal clinically significant [CS]) for each region (cornea, conjunctiva, anterior chamber, iris, lens, and eyelid) will be summarized for OD and OS separately for Visit 1, and Visit 2 before qualification ABC and post-treatment ABC. Shift from baseline to Visit 2 post-treatment ABC in the results will also be summarized. The analyses will be based on the Safety Set.

14.4.4 IOP

Actual values for IOP will be summarized for OD and OS separately by treatment group for Visit 1 and Visit 2. The analyses will be based on the Safety Set.

14.4.5 Dilated Fundoscopy

Dilated fundoscopic results (normal, abnormal NCS, abnormal CS) for each region (vitreous, retina, macula, optic nerve, and choroid) will be summarized for OD and OS separately for Visits 1 and 2. The analyses will be based on the Safety Set.

14.4.6 Peak Expiratory Flow Rate

Actual values for PEFR (predicted average PEFR, 80% of predicted value [derived], and PEFR value [derived]) will be summarized by treatment group for Visit 2, before qualification ABC®, 60 minutes during

qualification ABC®, 120 minutes post-instillation, 240 minutes post-instillation, 360 minutes post-instillation, and 480 minutes post-instillation. Change from baseline to each post-IP instillation time points will also be summarized. The analyses will be based on the Safety Set.

14.4.7 Vital Signs

Actual values for vital signs (pulse rate, systolic blood pressure, and diastolic blood pressure) will be summarized by treatment group for Visit 1 and Visit 2. Arm used (Right Arm, Left Arm) will also be summarized using number of subjects and percentages. The analyses will be based on the Safety Set.

15. Interim Analyses

No interim analysis is planned.

16. Changes to the Analyses Planned in the Protocol

Changes to the analyses that are planned in the protocol are described as below:

Item	Protocol	SAP	Rational for Change
1	Section 10.1.6: Intercurrent events for secondary efficacy analyses will be handled utilizing the same strategy for the primary efficacy analysis, with the following addition: 3. Discontinuation of study drug and non-optimal compliance will be ignored (that is, measured values will be used regardless of compliance or discontinuation of study drug) [treatment policy strategy].	Removed from the SAP	Not applicable as there was only one dose of study drug and efficacy measures on the date as the dosing date.
2	**Section 10.1.6:** Multiple imputation using randomized treatment-based regression methodology	**Section 8.2:** Multiple imputation using randomized, treatment-based Markov chain Monte Carlo (MCMC) methodology to impute non-monotone missing and using randomized treatment-based regression methodology to impute monotone missing.	If the missing data is not monotone, regression methodology would not work.

17. SAS® Example Codes for Multiple Imputations

Randomized, Treatment-Based MCMC Methodology to Impute Non-monotone Missing Data

The SAS® example codes for obtaining the imputed data for each endpoint.

```
PROC MI DATA = INDATA SEED = 7152 OUT = MDATA NIMPUTE = 20
                  BY TREATMENT;
                  MCMC IMPUTE=MONOTONE;
      VAR PRE_INSTILLATION POST10MIN POST300MIN POST60MIN POST360MIN POST420MIN
               POST480MIN;
RUN;
```

Randomized, Treatment-Based Regression Methodology for Monotone Missing Data

```
PROC MI DATA = MDATA SEED = 543245 OUT = OUTDATA NIMPUTE = 1
BY TREATMENT _IMPUTATION_;

*For each endpoints at 10 minute post-instillation;
MONOTONE REG(POST10MIN = PRE_INSTILLATION/ DETAILS);
VAR PRE_INSTILLATION POST10MIN;

*For each endpoints at 30 minute post-instillation;
MONOTONE REG(POST30MIN = PRE_INSTILLATION POST10MIN/ DETAILS);
VAR PRE_INSTILLATION POST10MIN POST30MIN;

*For each primary endpoints at 60 minute post-instillation;
MONOTONE REG(POST60MIN = PRE_INSTILLATION POST10MIN POST30MIN/ DETAILS);
VAR PRE_INSTILLATION POST10MIN POST30MIN POST60MIN;

*For each endpoints at 360 minute post-instillation;
MONOTONE REG(POST360MIN = PRE_INSTILLATION POST10MIN POST30MIN POST60MIN/
DETAILS);
VAR PRE_INSTILLATION POST10MIN POST30MIN POST60MIN POST360MIN;

*For each endpoints at 420 minute post-instillation;
MONOTONE REG(POST420MIN = PRE_INSTILLATION POST10MIN POST30MIN POST60MIN
POST360MIN / DETAILS);
VAR PRE_INSTILLATION POST10MIN POST30MIN POST60MIN POST360MIN POST420MIN;

*For each primary endpoints at 480 minute post-instillation;
MONOTONE REG(POST480MIN = PRE_INSTILLATION POST10MIN POST30MIN POST60MIN
POST360MIN POST420MIN / DETAILS);
VAR PRE_INSTILLATION POST10MIN POST30MIN POST60MIN POST360MIN POST420MIN
POST480MIN;

RUN;
```

18. References

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)

US Federal Register. (2021) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials E9(R1)

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. Revision History

This revision was issued following protocol 910, Amendment 2 dated 31Jul2023.

Section	Description of change	Rationale
Section 14.1.1	Change from *Treatment effects will be estimated and the statistical hypotheses will be tested **using two-sample tests assuming equal variances. Estimated mean differences** between treatment groups and associated 95% CI, and overall p-values will provided.* To *Treatment effects will be estimated and the statistical hypotheses will be tested using **an analysis of covariance (ANCOVA) model with the efficacy variable as the dependent variable, treatment as a factor, and corresponding baseline score as a covariate. Estimated least square mean** differences between treatment groups and associated 95% CI, and overall p-values will provided.*	Correction to the SAP
Section 14.1.2, Table 1, Sensitivity #1, Analysis Method(s)	Change from ***An analysis of covariance model (ANCOVA)*** To ***Two-sample t-tests***	Correction to the SAP
Section 14.1.2, Table 1, Sensitivity #2, 3, 4, & 5, Analysis Method(s)	Change from ***Two-sample t-tests assuming equal variances*** To ***Two-sample t-tests***	Correction to the SAP