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 for the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge Model

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
CAC	Conjunctival Allergen Challenge
Combo	Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution
CS	Clinically Significant
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
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)
PP	Per Protocol
PT	Preferred Term
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Treatment-Emergent Serious Adverse Event
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 909, Amendment 3.0 (Version 4.0) dated 03Apr2023.

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 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 3(±1), 5(±1), and 7(±1) minutes post-conjunctival allergen challenge (CAC; 0-4 scale, allowing half unit increments) at Visits 4b and 5
- Conjunctival redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

2.2.1.2 Secondary Efficacy Measures and Endpoints

- Ciliary redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

- Episcleral redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

2.2.1.3 Exploratory Efficacy Measures and Endpoints

- Eyelid swelling score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-3 scale, not allowing half unit increments) at Visits 4b and 5
- Tearing score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5
- Chemosis score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5

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

2.2.3 Tolerability Measures

- Ocular comfort grade (lowest score of the subject's two eyes) assessed by the subject upon investigational product instillation and at 1 minute (± 0.5 minutes) after investigational product instillation at Visit 4a (0-10 unit scale)
- Subject description of drop comfort questionnaire assessed at 3 minutes post-instillation at Visit 4a

2.3 Statistical Hypotheses and Adjustments for Multiplicity

Statistical success will be achieved if all of the following conditions are met at Visits 4b for duration of action and Visit 5 for onset of action:

- The Combo is superior in ocular itching and ocular redness to Vehicle.
- The Combo is superior in ocular itching to brimonidine tartrate 0.025%.
- The Combo is superior in ocular redness to ketotifen fumarate 0.035%.

Superiority will be demonstrated for the first bullet point above if all of the following are true.

- For each endpoint, the estimated treatment effect (of the difference between ketotifen fumarate/brimonidine tartrate Combo ophthalmic solution and vehicle) is at least 0.5 units (one step) on a 5-point (nine step) scale at all three post-CAC time points at each of Visit 4b and 5.
- For each endpoint, the estimated treatment effect is at least 1.0 unit (two steps) at two or three post-CAC time points at both Visits 4b and 5.
- For each endpoint at each visit, hypothesis testing will start with the first two post-CAC time points. If the treatment effect is statistically significant (one-sided α = 0.0125=0.025/2 to account for the two time points) at both post-CAC time points, then this condition is met. If the treatment effect is statistically significant at only one of the time points, then the third time point is tested at the unused one-sided alpha of 0.0125.

Superiority will be demonstrated for the second and third bullet points at the beginnng of Section 2.3 if all of the following are true.

- The estimated treatment effect (of the difference between ketotifen fumarate/brimonidine tartrate Combo ophthalmic solution and the comparator) is at least 0.5 units (one step) on a 5-point (nine step) scale at all three post-CAC time points at each of Visit 4b and 5.
- The estimated treatment effect is at least 1.0 unit (two steps) at two or three post-CAC time points at both Visits 4b and 5.
- At each visit, hypothesis testing will start with the first two post-CAC time points. If the treatment effect is statistically significant (one-sided α = 0.0125=0.025/2 to account for the two time points) at both post-CAC time points, then this condition is met. If the treatment effect is statistically significant at only one of the time points, then the third time point is tested at the unused one-sided alpha of 0.0125.

2.3.1 Hypotheses

Superiority Tests

For each primary endpoint at each of the six evaluation times, two superiority hypotheses will be tested comparing the Combo to a comparator (Vehicle and either ketotifen fumarate 0.035% or brimonidine tartrate 0.025%). The null hypothesis (H_0) is that the mean score for the subjects in the test (Combo) 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.

$$H_0: \mu_T \geq \mu_C$$
$$H_1: \mu_T < \mu_C$$

The hypotheses above will be tested for each of the six post-instillation times at Visits 4b and 5 (three post-instillation times per visit) using an ANCOVA model with terms for baseline value and treatment. Success will be determined as per the criteria described in Section 2.3.

Statistical inference will be performed for the secondary efficacy endpoints only if the primary efficacy endpoints demonstrate success and statistical inference for the secondary efficacy endpoints will be performed in a hierarchical manner in the order from the list of endpoints in Section 2.2.1.2. Success for each secondary endpoint will follow the same criteria as the primary endpoint. Sensitivity analyses for the secondary endpoints will be performed in the same manner as the sensitivity analyses for the primary endpoints.

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 6 study visits: a Screening Period of 3 study visits to verify subjects are eligible to participate and, following randomization, a Treatment Period of 3 study visits 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 an ocular allergen challenge titration using an allergen that elicited a positive reaction via skin testing. Subjects with a positive reaction post-CAC will undergo a confirmation CAC at Visit 3 with the same allergen qualified during Visit 2.

Treatment will begin at Visit 4a after subjects are randomized 1:1:1:1 to receive either Combo bilaterally, ketotifen fumarate 0.035% ophthalmic solution bilaterally, brimonidine tartrate 0.025% ophthalmic solution bilaterally, or vehicle ophthalmic solution bilaterally. At this visit, subjects will receive an in-office dose of the treatment they were randomized to receive. Approximately 8 hours post-instillation of study medication, at Visit 4b, subjects will undergo a CAC. Subjects will receive a final dose of study medication at Visit 5 approximately 15 minutes prior to CAC. Efficacy evaluations will be conducted at Visit 4b and Visit 5.

Table 1. Schedule of Visits and Assessments

Visit	Visit 1	Visit 2	Visit 3	Visit 4a	Visit 4b	Visit 5
Day	-52 to -22	-21±3	-14±3	1	(8 hours from Visit 4a)	15±3
PROCEDURE						
General Assessments						
Informed Consent & HIPAA[1]	X					
Demographic Data	X					
Medical & Medication History	X					
Update Medical & Medication History		X	X	X	X	X
Allergic Skin Test	X					
Urine Pregnancy Test		X		X		X
Review Incl./Excl. criteria	X	X	X	X		
Enrollment/Randomization				X		
AE (TEAE[2]) Assessment	X	X	X	X	X	X
Allergen Challenge						
Titration CAC		X				
Confirmation CAC			X			
8 Hour Duration of Action CAC					X	
15 Minute Onset of Action CAC						X
Signs and Symptoms Assessments[3]		X	X	X	X	X
Relief Drop Instillation[4]		X	X		X	X
Visual/Systems Exams						
Visual Acuity Utilizing an ETDRS chart		X	X	X	X	X
Slit Lamp Biomicroscopy		X	X	X	X	X
Intraocular Pressure		X				X
Dilated Fundoscopy		X				X
Investigational Product						
IP Instillation				X[5]		X[6]
Drop Comfort & Descriptor Assessment				X		

[1] In the event that a subject has a medical condition, medication/contact lens washout, or needs to speak with the Investigator prior to Visit 1, the subject will be given an informed consent form. Medical/medication history, demographics, skin test, and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).
[2] Applicable to Visits 4a (post IP instillation), 4b, and 5 only.
[3] Performed pre-CAC and post-CAC. Note: pre/post CAC is not applicable for Visit 4a.
[4] Relief medication may be administered to subjects at the end of Visits 2, 3, 4b, and 5, after all evaluations have been completed. Relief drop use should be recorded on the Concomitant medication log.
[5] 8 hour (+1 hour) pre-CAC.
[6] 15 (+1) minutes pre-CAC.

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 4a, they 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 40 subjects in each treatment group will have at least 98% power to detect a difference in means of 1 unit at each time point assuming that the common standard deviation (SD) is 1 unit using a two-group t-test with a 1.25% one-sided significance level. Given that both efficacy measures (itching and redness) must pass in order to declare success, the overall power is at least 96%. To allow for 10% dropouts, 45 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.

All study data will be listed by subject, treatment, and visit (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 additional decimal place than reported in the raw values. Standard deviations 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 one-sided with a significance level of 0.05 (α = 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 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].

Intercurrent events for secondary efficacy analyses will be handled utilizing the same strategy for the primary efficacy analysis, with the following addition:

- Discontinuation of study drug will be ignored (that is, measured values will be used regardless of compliance or discontinuation of study drug) [treatment policy strategy].

8.3 Other Missing or Inconclusive Data Handling

In general, there will be no 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

A summary for subject disposition by treatment group and overall for all subjects will include:

- Number of screen failures for all subjects only
- 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, deviations resulting excluding from PP Set, and COVID-19 related protocol deviations will be summarized by treatment group and overall for all subjects for the ITT Set.

A subject listing will be provided for protocol deviations that includes the visit at which the deviation occurred, the deviation date, 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, age in years at signing of ICF, age group (<65 years, ≥65 years), race, ethnicity, and iris color for OD and OS). Subjects who record more than one race are 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 at Screening will be summarized by treatment group. A subject listing will be provided for Allergic skin test results as well as the CAC titration and confirmation results performed at Visits 2 and 3, respectively.

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 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 summarized once for that SOC or PT

Medical history data will be presented in a subject listing.

13. Prior or Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug; Global B3, March 2022). Concomitant medications will be defined as medications used during 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. 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 separate subject listings.

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 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Conjunctival redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

Statistical success will be achieved if all of the following conditions are met at Visits 4b for duration of action and Visit 5 for onset of action:

- The Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution (Combo) is superior in ocular itching and ocular redness to Vehicle.
- The Combo is superior in ocular itching to brimonidine tartrate 0.025%.
- The Combo is superior in ocular redness to ketotifen fumarate 0.035%.

Each primary endpoint will be summarized at baseline and for each post-instillation of study drug time point at Visits 4b and 5 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 model (ANCOVA) with terms for baseline value and treatment. Estimated 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	ANCOVA	PP Set
2	The same as the primary analysis	two-sample t-tests assuming equal variances	ITT Set
3	Multiple imputation using a randomized, treatment-based MCMC for non-monotone missing and a randomized, treatment-based regression methodology for monotone missing	ANCOVA, two-sample t-tests assuming equal variances	ITT Set
4	Worst observation carried forward	ANCOVA, two-sample t-tests assuming equal variances, Wicoxon rank sum test	ITT Set
5	Observed values only	ANCOVA, two-sample t-tests assuming equal variances Wilcoxon rank sum test,	ITT Set, FAS, PP Set

Note: ANCOVA model has the terms treatment and baseline value.

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 #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:

- Ciliary redness score (average score of the subject‘s two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Episcleral redness score (average score of the subject‘s two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

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 #5 (Table 2) for subgroup of age (<65 vs ≥65 years), sex (male vs female), and race (white vs others).

14.3 Analyses of Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- Eyelid swelling score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-3 scale, not allowing half unit increments) at Visits 4b and 5
- Tearing score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5
- Chemosis score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5

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 Baseline, Visit 4b, and Visit 5. Change from baseline to Visit 4b and Visit 5 will also be summarized. 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 baseline, Visit 4b, and Visit 5. Shift from baseline to Visit 4b and Visit 5 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 Baseline and Visit 5. Change from baseline to Visit 5 will also be summarized. 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 baseline and Visit 5. Shift from baseline to Visit 5 in the results will also be summarized. The analyses will be based on the Safety Set.

14.5 Analyses of Tolerability Measures

14.5.1 Ora Calibra® Drop Comfort Assessment and Questionnaire

Ora Calibra® Drop Comfort Assessment and Questionnaire will be performed at Visit 4a. Drop Comfort Assessment will be performed for 3 time points: immediately upon instillation, 1 minute post-instillation, 2 minutes post-installation. Drop Comfort score is ranged from 0 to 10, not allowing half unit increments. For the Drop Comfort Questionnaire, assessed at 3 minutes post-instillation, subjects will select three words (from options of burning, comfortable, cool, filmy, gentle, gritty, irritating, refreshing, smooth, soothing, sticky, stinging, and other) that best describe how each eye drop feels in both eyes.

Drop Comfort score will be summarized continuously by treatment group for each time point. For the Drop Comfort Questionnaire, number and percentages of subjects who selected any word will be summarized by treatment group and word for each time point. 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

No changes to the analyses that are planned in the protocol.

17. SAS® Codes for Multiple Imputations

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

The SAS® code for obtaining the imputed data will be dependent on the endpoint.

```
PROC MI DATA = INDATA SEED = 7152 OUT = MDATA NIMPUTE = 20
                        MINIMUM = 0 MAXIMUM = 4;
                        BY TREATMENT;
                        MCMC IMPUTE=MONOTONE;
    * For each primary endpoints at 3 minute post-CAC;
        VAR BASE_POST3MIN V4b_POST3MIN V5_POST3MIN;

    * For each primary endpoints at 5 minute post-CAC;
        VAR BASE_POST5MIN V4b_POST5MIN V5_POST5MIN;

    * For each primary endpoints at 7 minute post-CAC;
        VAR BASE_POST7MIN V4b_POST7MIN V5_POST7MIN;

    * For each secondary endpoints at 7 minute post-CAC;
        VAR BASE_POST7MIN V4b_POST7MIN V5_POST7MIN;

    * For each secondary endpoints at 15 minute post-CAC;
        VAR BASE_POST15MIN V4b_POST15MIN V5_POST15MIN;

    * For each secondary endpoints at 20 minute post-CAC;
        VAR BASE_POST20MIN V4b_POST20MIN V5_POST20MIN;
RUN;
```

17.2 Randomized, Treatment-Based Regression Methodology for Monotone Missing Data

```
PROC MI DATA = MDATA SEED = 543245 OUT = OUTDATA NIMPUTE = 1
MINIMUM = 0 0 0
MAXIMUM = 4 4 4
BY TREATMENT _IMPUTATION_;
    * For each primary endpoints at 3 minute post-CAC;
        MONOTONE REG(V4b_POST3MIN = BASE_POST3MIN/ DETAILS);
        MONOTONE REG(V5_POST3MIN = BASE_POST3MIN V4b_POST3MIN/ DETAILS);
        VAR BASE_POST3MIN V4b_POST3MIN V5_POST3MIN;

    * For each primary endpoints at 5 minute post-CAC;
        MONOTONE REG(V4b_POST5MIN = BASE_POST5MIN/ DETAILS);
        MONOTONE REG(V5_POST5MIN = BASE_POST5MIN V4b_POST5MIN/ DETAILS);
        VAR BASE_POST5MIN V4b_POST5MIN V5_POST5MIN;

    * For each primary endpoints at 7 minute post-CAC;
        MONOTONE REG(V4b_POST7MIN = BASE_POST7MIN/ DETAILS);
        MONOTONE REG(V5_POST7MIN = BASE_POST7MIN V4b_POST7MIN/ DETAILS);
        VAR BASE_POST7MIN V4b_POST7MIN V5_POST7MIN;

    * For each secondary endpoints at 7 minute post-CAC;
        MONOTONE REG(V4b_POST7MIN = BASE_POST7MIN/ DETAILS);
        MONOTONE REG(V5_POST7MIN = BASE_POST7MIN V4b_POST7MIN/ DETAILS);
        VAR BASE_POST7MIN V4b_POST7MIN V5_POST7MIN;
```

```
    * For each secondary endpoints at 15 minute post-CAC;
        MONOTONE REG(V4b_POST15MIN = BASE_POST15MIN/ DETAILS);
        MONOTONE REG(V5_POST15MIN = BASE_POST15MIN V4b_POST15MIN/ DETAILS);
        VAR BASE_POST15MIN V4b_POST15MIN V5_POST15MIN;

    * For each secondary endpoints at 20 minute post-CAC;
        MONOTONE REG(V4b_POST20MIN = BASE_POST20MIN/ DETAILS);
        MONOTONE REG(V5_POST20MIN = BASE_POST20MIN V4b_POST20MIN/ DETAILS);
        VAR BASE_POST20MIN V4b_POST20MIN V5_POST20MIN;
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)

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