STATISTICAL ANALYSIS PLAN

A Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy and Safety of SI-614 Ophthalmic Solution in Patients with Dry Eye (The SIDE Study)

Version 2.0 30MAY2023

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Protocol Number: 614/1132

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Statistical Analysis Plan Approval

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List of Abbreviations

Abbreviation	Definition
ADaM	Analysis Dataset Model
AE	Adverse Event
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
[redacted]	[redacted]
CFB	Change from Baseline
CI	Confidence Interval
CS	Clinically Significant
COVID-19	Coronavirus Disease 2019
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IP	Investigational Product
ITT	Intention-to-Treat
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
MMRM	Mixed-Model Repeated Measures
MNAR	Missing Not at Random
NCS	Not Clinically Significant
OSDI	Ocular Surface Disease Index
PDF	Portable Document Format
PMM	Pattern Mixture Model
PP	Per-Protocol
PT	Preferred Term
QID	*Quater in die* (Four Times Daily)
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class

Abbreviation	Definition
tCFS	Total Corneal Fluorescein Staining
TE-SAE	Treatment-Emergent Serious Adverse Event
TEAE	Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
TMF	Trial Master File
WHODrug	World Health Organization Drug Dictionary

1 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting in detail for the efficacy and safety assessments of study 614/1132 as well as relevant data collected in protocol 614/1132, Version 1.0 dated 23MAR2022.

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, the most recent ICH E9 (R1) Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials, and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2 Study Objectives

The objective of this study is to evaluate the efficacy and safety of 0.3% SI-614 ophthalmic solution compared with placebo when administered 4 times daily (QID) for 84 days in patients with dry eye.

3 Study Design and Procedures

3.1 General Study Design

This study is a Phase 3, multicenter, randomized, double-masked study to evaluate the efficacy and safety of 0.3% SI-614 Ophthalmic Solution compared to placebo in patients with dry eye. Approximately 230 patients will be randomized with a ratio of 1:1 into one of the two groups: (1) 0.3% SI-614, or (2) placebo, which they will be instructed to administer QID for 84 days. The randomization will be stratified by two factors:

- Average of dryness and ocular discomfort at bedtime assessment based on run-in patient daily diary mean from Day-7 through Day -1: ≤2.5 vs >2.5
- Change [redacted] in total corneal fluorescein staining at Visit 2: ≤3.5 vs. >3.5

Table 1 shows the scheduled study visits, their planned study day (note that there is no Day 0 and that Day 1 corresponds to the day of randomization), and the acceptable visit window for each study visit:

Table 1. Study Visit Windows

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -14	± 3 Days
Visit 2	Day 1	N/A
Visit 3	Day 8	± 2 Days
Visit 4	Day 15	± 2 Days
Telephone Visit 1	Day 22	± 2 Days
Visit 5	Day 29	± 3 Days
Telephone Visit 2	Day 43	± 2 Days
Visit 6	Day 57	± 3 Days
Telephone Visit 3	Day 71	± 2 Days
Visit 7	Day 85	± 3 Days

3.2 Schedule of Visits and Assessments

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

4 Study Variables

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the following:

- Change from baseline (CFB) [redacted] to Day 29 [redacted] in total corneal fluorescein staining (tCFS) score on the [redacted] Scale in the study eye.
    - Fluorescein staining will be conducted at all visits, including all [redacted] time points.
        - Grading of the [redacted] region will be conducted using the [redacted] Corneal and Conjunctival Staining Scale, which is a 0 to 4 scale [redacted] and where grade 0 = No Staining and 4 = Confluent Staining.
    - The tCFS score is derived using the sum of the [redacted] regions such that possible scores range from 0 to 12.

4.1.1 Statistical Hypotheses of Primary Endpoint

The statistical hypotheses are stated in terms of one-sided hypotheses, at a significance level of 0.025.

H_{01}: The change from baseline Visit 2 (Day 1, [redacted] to Visit 5 (Day 29, [redacted] in tCFS score [redacted] of the study eye for 0.3% SI-614 is equal or greater than placebo.

H_{A1}: The CFB Visit 2 (Day 1, [redacted] to Visit 5 (Day 29, [redacted] in tCFS score [redacted] of the study eye for 0.3% SI-614 is less than placebo.

4.1.2 ESTIMANDS

- **Estimand 1**: If the rate of intercurrent events such as lack of efficacy or adverse events (AEs) for the primary endpoint is balanced between the two treatment groups (as evaluated by the Fisher's exact test at an alpha level of 0.05) and the rate of intercurrent events for the endpoint is ≤ 5% in all patients, the intercurrent events for the primary analysis will be handled using Estimand 1. The proposed strategies listed in Estimand 1 for the primary analyses will potentially provide a relatively conservative treatment effect based on the assumptions associated with each intercurrent event.

  The rate of intercurrent events for primary efficacy endpoint will be summarized by treatment group and overall, with Fisher's exact test p-value.

  The following intercurrent events will be considered in Estimand 1:

  - Non-optimal compliance is ignored. Measures will be analyzed regardless of treatment compliance [treatment policy strategy], assuming the non-compliance is not associated with the assigned treatments.
  - Use of prohibited concomitant medications is ignored. Measures obtained after use of prohibited concomitant medications will be analyzed [treatment policy strategy], assuming more patients from the placebo group would experience this intercurrent event.
  - Treatment discontinuation due to lack of efficacy before the assessment of the primary endpoint. Missing values assumed to be missing not at random (MNAR) will be multiply imputed using placebo group-based pattern mixture model (PMM) imputation [hypothetical strategy], assuming more patients in the placebo group would experience this intercurrent event.
  - Treatment discontinuation due to AEs before the assessment of the primary endpoint. Missing values assumed to be missing not at random (MNAR) will be imputed using placebo group-based pattern mixture model (PMM) imputation [hypothetical strategy], assuming more patients in the treatment group would experience this intercurrent event.
  - Treatment discontinuation due to reasons other than lack of efficacy or AEs, assumed to be missing at random (MAR), will be multiply imputed using randomized treatment group-based Markov Chain Monte Carlo (MCMC) imputation. [hypothetical strategy]

- Five subjects were randomized using incorrect stratification data at Visit 2, resulting mis-randomization if correct strata were used. Those subjects will be analyzed as randomized with the correct baseline information.

- **Estimand 2**: If the rate of intercurrent events such as lack of efficacy or AEs for the endpoint is imbalanced between treatment groups (demonstrated by Fisher's exact test with a p-value of <0.05) and the rate of intercurrent events for the endpoint is greater than 5% in all patients, then the primary analyses will utilize ITT population with Estimand 2. The trimmed mean approach will be applied to the primary analyses. The patients' data, missing or non-missing, will be trimmed if the patients experience the intercurrent events such as treatment discontinuation due to lack of efficacy or treatment discontinuation due to AEs. The permutation test will be used to test the treatment difference. The trimmed proportion is as shown on Table 2.

Table 2. Proportions of Data Trimmed

Maximum Rate of intercurrent events in any treatment group (%)	Data Trimmed (%)
5% to <10%	10%
10% to <20%	20%
20% to <30%	30%

The following intercurrent events will be considered in Estimand 2:

- Treatment discontinuation due to lack of efficacy or AEs before the assessment of the primary endpoint – will be trimmed irrespective of missingness or not
- Missing data as results of treatment discontinuation due to reasons other than lack of efficacy or AEs, assumed to be MAR, will be multiply imputed using randomized treatment group-based MCMC imputation. [hypothetical strategy]
- Non-optimal compliance is ignored. Measures will be analyzed regardless of treatment compliance [treatment policy strategy], assuming the non-compliance is not associated with the assigned treatments.
- Use of prohibited concomitant medications is ignored. Measures obtained after use of prohibited concomitant medications will be analyzed [treatment policy strategy]
- Subjects who were mis-randomized will be analyzed as randomized using the correct baseline information.

4.2 Secondary Endpoint

The secondary efficacy endpoint is the following:

- CFB (Day -7 through Day -1) in the average score of ocular discomfort and dryness on the [redacted] Ocular Discomfort & 4-Symptom Questionnaire at the bedtime assessment from the patient daily diary during Day 1 through Day 14
    - Each day during the at-home dosing period, patients will grade the severity of their DED symptoms in their diary before instilling the study drug at their morning and evening doses.
        - The [redacted] Ocular Discomfort & 4-Symptom Questionnaire will be used, which includes rating the severity of 5 symptoms: ocular discomfort, burning, dryness, grittiness, and stinging. Each symptom rating ranges from 0 to 5 using whole numbers, where 0 = None and 5 = Worst.
    - The CFB is calculated as the average score of ocular discomfort and dryness of the study day minus the baseline value (as defined in Section 9.3)

4.2.1 Statistical Hypotheses of Secondary Endpoint

The statistical hypotheses are stated in terms of one-sided hypotheses, at a significance level of 0.025.

H_{02}: The CFB (Day -7 through Day -1) in the average score of ocular discomfort and dryness at the bedtime assessment from the Patient Daily Diary during Day 1 through Day 14 for 0.3% SI-614 is equal or greater than placebo.

H_{A2}: The CFB (Day -7 through Day -1) in the average score of ocular discomfort and dryness at the bedtime assessment from the Patient Daily Diary during Day 1 through Day 14 for 0.3% SI-614 is less than placebo.

4.3 Exploratory Endpoints

The exploratory efficacy endpoints are the following:

Signs:

- Fluorescein staining score on the [redacted]
    - [redacted]
    - [redacted]
    - [redacted] will also be derived and analyzed.
- Lissamine green staining score on the [redacted]
    - Lissamine green staining will be assessed in each eye at all visits for all [redacted] time points.
        - Grading of the [redacted] regions will be conducted using [redacted] Corneal and Conjunctival Staining Scale from 0 to 4 [redacted] where grade 0 = No Staining and 4 = Confluent Staining.
    - [redacted]
    - [redacted]

- [redacted] will also be derived and analyzed.

- Tear film break-up time (TFBUT)
  - TFBUT will be assessed in each eye at all visits for all [redacted] time points.
    - For each eye, two measurements will be recorded in seconds and averaged unless the two measurements are >2 seconds apart and are each <10 seconds, in which case, a third measurement will be taken and the two closest of the three will be averaged and used for analyses. If the differences between two sequential pairs of measurements are the same (e.g., 3, 6, 9 seconds), then the median of the three readings will be used for analysis.
- Conjunctival redness on [redacted] Scale
  - Conjunctival redness using the [redacted] Conjunctival Redness Scale will be assessed in each eye at all visits for all [redacted] time points.
    - The conjunctival redness scale ranges from 0 to 4 where 0 = Normal, [redacted] and 4 = [redacted] Analyses will be for study eye only.

<u>Symptoms</u>:

- Patient daily diary during the dosing period
  - On each day during the at-home dosing period, patients will grade the severity of their DED symptoms in their diary in the morning and in the evening before instilling the study drug. [redacted] Ocular Discomfort & 4-Symptom Questionnaire will be used, which includes rating the severity of 5 symptoms at the subject level: ocular discomfort, burning, dryness, grittiness, and stinging. Each symptom rating ranges from 0 to 5, where 0 = None and 5 = Worst.
- Ocular Surface Disease Index (OSDI) questionnaire
  - The OSDI is assessed on a scale of 0 to 100, with higher scores representing greater disability. The OSDI asks the following 12 questions at the subject level:

    Have you experienced any of the following during the last week:

    (1) Eyes that are sensitive to light?
    (2) Eyes that feel gritty?
    (3) Painful or sore eyes?
    (4) Blurred vision?
    (5) Poor vision?

    Have problems with your eyes limited you in performing any of the following during the last week:

(6) Reading?

(7) Driving at night?

(8) Working with a computer or bank machine (ATM)?

(9) Watching TV?

Have your eyes felt uncomfortable in any of the following situations during the last week:

(10) Windy conditions?

(11) Places or areas with low humidity (very dry)?

(12) Areas that are air conditioned?

The OSDI will be assessed at each visit, including all [redacted] time points. The total OSDI score is calculated by the following:

$$\text{OSDI} = \frac{(\text{Sum of Scores}) \times 25}{\#\text{ of Questions Answered}}$$

Note that the number of questions answered in the denominator should exclude questions with a response of "N/A". OSDI will be analyzed for total OSDI score and subtotal scores (i.e., OSDI questions 1-5, OSDI questions 6-9, and OSDI questions 10-12).

- [redacted] Ocular Discomfort and 4-Symptom Questionnaire
  - As described in the assessment description for the "Patient daily diary during the dosing period" endpoint
- [redacted] Ocular Discomfort Scale
  - Ocular discomfort will be assessed in each eye using the [redacted] Ocular Discomfort Scale at all visits, including [redacted] time points.
    - For the [redacted] time point, patients will rate their ocular discomfort [redacted] The Ocular Discomfort Scale ranges from 0 to 4 where 0 = No discomfort, [redacted] and 4 = Constant discomfort.

4.4 Safety Variables

The safety endpoints include the following:

- AEs
- Best-corrected visual acuity (BCVA)
  - The logarithm of the minimum angle of resolution (logMAR) BCVA will be assessed [redacted] at each visit, as well as [redacted] at Visit 3 (Day 8), using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Patients should use their most recent correction to attain their BCVA.

- Slit-lamp biomicroscopy
    - A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, and lid will be performed at each visit, including all [redacted] time points. The examination consists of a categorical determination of each region graded as Normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS).

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Groups

Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1 (Day -14) and Visit 2 (Day 1) will be assigned a randomization number at the end of Visit 2 (Day 1). The Interactive Web Response System (IWRS) will be used to assign all randomization numbers and kit numbers will be to each subject as they are entered into the IWRS.

The site staff will dispense each kit required until the next visit. Both the randomization number and the dispensed study drug kit number will be recorded on the subject's source document and electronic case report form (eCRF).

5.2 Masking and Unmasking

All patients, investigators, and study personnel, including Sponsor, [redacted] and [redacted], involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment group has been assigned to a subject. When possible (i.e., in non-emergent situations), [redacted]. and/or the study Sponsor should be notified before unmasking study drug. [redacted] and/or the study Sponsor must be informed immediately about any unmasking event.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, they should contact [redacted] and/or the medical monitor prior to unmasking the identity of the investigational product (IP), if possible. [redacted] will ask the site to complete and send them the Unmasking Request Form. [redacted] will notify the Sponsor and jointly will determine if the unmasking request should be granted. They may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. The investigator will unmask the subject's treatment assignment using IWRS upon approval of request. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the Trial Master File (TMF). For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject must be noted in the subject's study file.

Unmasked patients will be discontinued from the study. Unmasked patients will be followed for safety monitoring until resolution of the AE or study completion, whichever occurs last.

6 Sample Size and Power Considerations

In order to detect a difference of -0.75 for the primary endpoint between 0.3% SI-614 and placebo with 90% power and accounting for an assumed 5% drop-out rate, 115 patients are required to be randomized per treatment group. This assumes a two-sided test at alpha = 0.05 and a common standard deviation (SD) of 1.7.

The power and sample size for this study were calculated and based upon the results from the previous Phase 2 (Protocol # 614/1121) and Phase 2/3 study (Protocol # 614/1131).

7 Data Preparation

7.1 Input Data

Study data will primarily be recorded on the eCRFs supplied by [redacted] using [redacted]

When all prerequisites for database lock have been met, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with [redacted].

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

- Database lock has occurred with written authorization provided by appropriate [redacted] and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations) prior to database lock.
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

7.2 Output Data

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

SDTM will follow the SDTM version 1.7 model and will be implemented using the SDTM Implementation Guide version 3.3 and the SDTM Controlled Terminology version 2022-03-25. ADaM data will follow the ADaM version 2.1 model and will be implemented using the ADaM Implementation Guide version 1.1. Both SDTM and ADaM will be validated using Pinnacle 21. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

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

8 Analysis Populations

8.1 Intention-to-Treat Population

The Intention-to-Treat (ITT) population includes all randomized patients. Patients in the ITT population will be analyzed as randomized.

8.2 Per-Protocol Population

The Per-Protocol (PP) population is defined as all ITT patients who have no major protocol deviations and who complete the trial. Protocol deviations will be assessed prior to database lock and unmasking. Patients in the PP population will be analyzed as treated.

8.3 Safety Population

The Safety population includes all randomized patients who have received at least one dose of study drug. Patients in the Safety population will be analyzed as treated.

9 General Statistical Considerations

9.1 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the study eye, as defined by the following:

Study Eye: Eyes are eligible for analysis if they meet all inclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with the greatest change from [redacted] to [redacted] (i.e., [redacted] minus [redacted] in corneal total fluorescein staining score (sum of [redacted] regions) at baseline (Visit 2). If the baseline change from [redacted] to [redacted] in corneal total fluorescein staining score is the same in both eyes, then the right eye will be used as the study eye. If only one eye meets all inclusion criteria, then the single qualifying eye is the study eye.

9.2 Missing or Inconclusive Data Handling

Missing data for the primary efficacy endpoints will be imputed as specified as follows:

- For MAR, the data will be imputed using treatment-group based MCMC on the ITT population
- For MNAR due to intercurrent events, the imputation methods are defined in Section 4.1.2 for estimands.

The rate of intercurrent events for primary efficacy endpoint will be summarized by treatment group and overall, with Fisher's exact test p-value.

Imputation of missing data will be executed 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 first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, 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 unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
  Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is “No” then the missing end date will be imputed as the last dose date.
- 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.).

9.3 Definition of Baseline

Baseline measure for the primary efficacy endpoint is defined as pre-randomization measurement taken at Visit 2 (Day 1, [redacted] If a measure is taken both [redacted] and [redacted] the baseline will be the time-point-matched measure at Visit 2 (Day 1). For changes from [redacted] to [redacted] after the first treatment, the change from [redacted] to [redacted] at Visit 2 (Day 1) will be considered the baseline value.

For measures from patient daily diaries in the secondary and exploratory endpoints, baseline is defined as the average of all days during Day -7 to Day -1, calculated separately for the morning, bedtime, and daily averages. Daily scores are first obtained by averaging the AM and PM scores for that day, as applicable.

9.4 Data Analysis Conventions

All data analysis will be performed by [redacted] after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS Version

9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation.

Summaries for continuous and ordinal variables will include the number of observations (n), mean, SD, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means, confidence intervals (CI), and medians will be presented to one additional decimal place than reported in the raw values. SDs will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include counts and percentages. CFB will be calculated as follow-up visit value minus baseline value. Differences between active treatment and placebo groups will be calculated as active minus placebo.

All statistical tests will be two-sided at a significance level of 0.05 unless otherwise specified. CIs for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to 3 decimal places; p-values less than 0.001 will be presented as “<0.001”; p-values greater than 0.999 will be presented as “>0.999.”

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit. All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized patients unless otherwise specified.

9.5 Adjustments for Multiplicity

Hierarchical fixed sequence testing strategy will be used in the analysis of the primary dry eye sign endpoint and the secondary dry eye symptom endpoint to maintain study-wide Type I error at one-sided 0.025. If the primary endpoint is statistically significant, then the study will be declared a success for the primary endpoint, and the secondary endpoint will be evaluated. If the primary endpoint analysis is not statistically significant, no claim will be made for the secondary endpoint.

10 Disposition of Patients

Patient disposition will be presented in terms of the numbers and percentages of patients who were screened and who screen failed; who were randomized; who were included in each analysis population (ITT, PP, and Safety); and who completed the study, discontinued from the study, and discontinued from the study due to COVID-19. Disposition will be summarized by treatment group and the overall total for all screened patients. Percentages will be calculated using all randomized patients as the denominator unless otherwise specified.

The reasons for premature study discontinuation, both general and COVID-19 related, will be summarized by treatment group and the overall total for all randomized patients and include: AEs, protocol violation, administrative reasons, lack of efficacy, lost to follow-up, pregnancy, sponsor termination of study, withdrawal by subject, and other. Percentages will be calculated using randomized patients as the denominator. A patient listing will be provided that includes the date of and reason for premature study discontinuations.

The number and percentage of patients with any deviation, major deviation, and minor deviation will be summarized by treatment group as well as overall total for all randomized patients. The protocol deviations that will be summarized include the following categories: Informed Consent, Inclusion/Exclusion and Randomization, Test Article / Study Drug Instillation and Assignment at Site, Improper Protocol Procedures at Site (Missed, Repeated, Not Per Protocol), Site's Failure to Report SAE (Serious AE) / AE, Visit out of Window (Missed, Early, Late), Subject's Non-compliance with Test Article / Study Drug, Subject's use of Prohibited Concomitant Medication, Subject's Failure to Follow Instructions, and Other. A subject listing will be provided that includes the date of the deviation, visit at which the deviation occurred, the deviation code, the deviation description, the action taken, if the deviation was COVID-19 related, and the classification of whether the deviation was judged to be major or minor in a masked review.

In addition, subject listings will be provided that include randomization schedule details, informed consent date, inclusion and exclusion criteria violations, and exclusions from the analysis populations.

11 Demographic and Pretreatment Variables

11.1 Demographic Variables

The demographic variables collected in this study include age, sex (childbearing potential), race, ethnicity, and iris color. Patients who record more than one race will select Other and specify their racial identities.

Iris color will be summarized by OD and OS. Demographic variables will be summarized separately for the ITT, PP, and Safety populations.

Age (years) will be summarized, by treatment group and the overall total among all patients in the respective summary population, using continuous descriptive statistics (number of patients [n], mean, SD, median, minimum, and maximum). Age will also be categorized as follows: < 65 years and ≥ 65 years. Age will be reported in years and calculated using the following formula:

$$\text{Age} = (\text{Informed Consent Date} - \text{Date of Birth}) / 365.25$$

The number and percentage of patients will be presented, overall and by treatment, for age category, sex, race, ethnicity, iris color, and childbearing potential (among female patients).

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

11.2 Baseline Disease Characteristics

Baseline disease characteristics will be summarized for all assessments including tCFS and fluorescein staining, ocular discomfort and dryness bedtime average, [redacted] Ocular Discomfort & 4-Symptom Questionnaire, lissamine green staining, TFBUT, conjunctival redness, total and subtotal OSDI score, and [redacted] Ocular Discomfort Scale by region, symptom, or question where relevant. Summaries will be presented for the study eye only for assessments used in efficacy endpoints except ocular discomfort & 4-symptom questionnaire and OSDI efficacy endpoints for subject-level. Continuous endpoints will be

summarized using continuous descriptive statistics (number of patients (n), mean, SD, median, minimum, and maximum). Baseline disease characteristics will be summarized separately for the ITT, PP, and Safety populations.

12 Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

The number and percentage of patients with ocular and non-ocular medical history will be summarized separately and presented by treatment group and overall total at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. If a subject reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. SOCs will be displayed in internationally agreed order and PTs within a SOC will be listed in order of descending frequency across all patients.

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

12.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global (B3, March 2022) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then the next lowest classification that is provided in the coding dictionary will be used.

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

Ocular and non-ocular concomitant medications will be summarized using the ITT population. Medications will be tabulated for each treatment group and overall total using frequencies and percentages. Patients may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if they report one or more medications. Percentages will be based on the number of patients in each treatment group. ATC classes will be listed in order of alphabetically and will be displayed with ATC text. Preferred names within an ATC class will be listed in descending frequency across all patients.

Listings of concomitant medications will be generated separately for ocular and non-ocular concomitant medications for all randomized patients.

12.3 Concomitant Procedures

Concomitant procedures/surgeries data will be coded using MedDRA v25.0. A listing of concomitant procedures/surgeries will be provided separately for ocular and non-ocular data for all randomized patients.

13 Dosing Compliance and Treatment Exposure

Subject listings will be produced for run-in and study drug assignment, instillation, and accountability.

13.1 Dosing Compliance

Patients will be instructed on proper use of the patient daily diary and proper instillation and storage of study drug at the end of Visit 1 (Day -14) through Visit 6 (Day 57) and given written instructions.

To account for diary entries that may be made after midnight nominally for the preceding evening, an evening diary entry with a dosing time on or after midnight but before 3 AM will be summarized as an entry for the preceding evening.

In the patient symptom daily diary, if more than 25% of applicable Dose Taken boxes are checked “No”, left blank, or missing for a diary period, that patient will be deemed non-compliant and a dosing deviation will be recorded. These guidelines will be used by the Investigator for determining the patient’s necessary compliance for the study and for recording deviations from this compliance.

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

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

The number of actual doses received will be calculated as the sum of the number of doses reported in the diary, plus the dose reported in the Study Drug Assign/Instill eCRF. If a subject received study drug in one eye but not the other, the subject will be counted as having dosed at that visit.

The number of expected doses that will be used for calculating compliance will be calculated as:

$$\text{Number of Expected Doses} = 4 \times [\text{Date of Last Dose} - \text{Date of Visit 2 (Day 1)} + 1]$$

for all patients.

A categorical dosing compliance variable will also be derived for <75%, 75% to 125%, >125%, where the category, 75% to 125%, is considered compliant.

Dosing compliance (%) will be summarized with continuous descriptive statistics (number of patients [n], mean, SD, median, minimum, and maximum) for each treatment group and for all patients using the Safety population. The compliance categories defined above will be summarized categorically with counts and percentages of those who were non-compliant, compliant, and over-compliant.

A subject listing of dosing compliance as well as treatment exposure (described below) will also be produced for all randomized patients.

13.2 Treatment Exposure

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

Extent of Exposure (days) = [Date of Last Dose – Date of Visit 2 (Day 1)] + 1

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

Extent of Exposure (days) = [Date of Last Recorded Visit – Date of Visit 2 (Day 1)] + 1

Extent of treatment exposure for each subject exposed to study drug will be summarized with continuous descriptive statistics (number of patients (n), mean, SD, median, minimum, and maximum) for each treatment group and overall total for all patients using the Safety population. Additionally, total exposure in days will be summarized for each treatment group and overall total for all patients.

14 Efficacy Analyses

14.1 Primary Efficacy Endpoint

14.1.1 Primary Analysis Methods

Primary analysis of the CFB [redacted] to Day 29 [redacted] in tCFS will be performed using an Analysis of Covariance(ANCOVA) model adjusted for baseline value with treatment group as the explanatory variable on ITT population with Estimand 1 or ITT population with Estimand 2 depending on the rate of intercurrent events. Least squares (LS) means for each treatment group and the LS mean difference comparing 0.3% SI-614 with placebo will be presented from the model together with SEs, two-sided 95% CIs, and one-sided p-values.

Subject listings will be provided for the primary efficacy endpoint for all randomized patients.

14.1.1.1 Imputation Methodology

According to Estimand 1 in Section 4.1.2, patients with intercurrent event for the primary endpoint will have their missing data imputed using placebo group-based PMM imputation when the intercurrent events are due to lack of efficacy or AEs, and randomized treatment group-based MCMC imputation when the missingness is due to reasons other than lack of efficacy or AEs.

The rate of intercurrent events for primary efficacy endpoint will be summarized by treatment group and overall, with Fisher's exact test p-values.

Missing data will be imputed for individual staining regions. TCFS scores will then be derived using the observed and imputed.

14.1.2 SENSITIVITY ANALYSES OF PRIMARY EFFICACY ENDPOINT

In addition to the primary analysis using Estimand 1 or Estimand 2 in ITT population, sensitivity analyses will be conducted using Estimand 1 or Estimand 2 in PP population. Analyses using observed data only will be conducted using both ITT and PP populations.

Sensitivity analyses for the primary efficacy endpoint will also be conducted using an Analysis of Variance (ANOVA) model adjusting for the stratification factors for randomization and the treatment indicator using ITT population with Estimand 1 or Estimand 2. In the ANOVA model, the randomized stratification data for the five subjects who were mis-randomized will be used. The same ANOVA model will also be performed using the correct stratification data for the five subjects.

Sensitivity analyses of the primary efficacy endpoint will also be performed on ITT population with multiple imputation by placebo group-based PMM, ITT population with multiple imputation via randomized treatment-group-based MCMC. Furthermore, a sensitivity analysis will be performed on the ITT population using last observation carried forward (LOCF) imputation where the last non-missing staining value will be carried forward (including baseline values if post-baseline values are not observed). Similar to the methods described above, the staining scores of each region will be carried forward, and then tCFS will be derived and changes from baseline will be calculated.

As an additional sensitivity analysis, tipping point analyses will be conducted to assess the robustness of the primary analyses. In tipping point analyses, a set of shift parameters will be added to the imputed missing values to re-evaluate the primary analyses conclusion under MNAR assumption. A tipping-point that overturns the statistical significance level will be identified. If the shift parameter is so extreme that it is considered clinically implausible, then this indicates robustness to missing data assumptions (MJ, Gorst-Rasmussen A, Tarp-Johansen).

Sensitivity analyses of the primary efficacy endpoint will be conducted using both ITT and PP populations.

14.1.3 SUPPORTIVE ANALYSES OF PRIMARY EFFICACY ENDPOINT

As supportive analyses, two-sample t-tests and Wilcoxon rank sum tests will be performed on the ITT population to compare the CFB to Visit 5 (Day 29) [redacted] between 0.3% SI-614 and placebo. The differences in means, standard errors (SEs), two-sided 95% CIs, and one-sided p-values will be reported at each time point. The exploratory comparisons between treatment groups at baseline and Day 29 in t CFS will be performed on ITT population with Estimand 1 or Estimand 2.

14.1.4 FIGURES

Mean CFB [redacted] to follow-up visits [redacted] in tCFS score [redacted] will be displayed graphically over time by line chart with SD by treatment group.

14.2 Secondary Efficacy Endpoints

14.2.1 Primary Analysis Methods

Average scores of ocular discomfort and dryness at the bedtime assessment and CFB will be calculated and summarized for each study day from Day 1 to Day 14.

Analyses of the secondary efficacy endpoint of the CFB (Day -7 through Day -1) in average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14 will be conducted using a mixed-model repeated measures (MMRM) on ITT population with observed data only. The model will include the baseline average score of ocular discomfort and dryness (average of Day -7 through Day -1), treatment group, study day (Day 1 to Day 14 as categorical variables), and the interaction between treatment group and study day as fixed effects with correlated errors due to study day. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a compound symmetry covariance will be used. The overall treatment differences (0.3% SI-614 versus placebo) in least squares means, 95% CI, and the corresponding p-values will be estimated based on the MMRM. Least squares means, standard errors, and 95% Cis will also be estimated for Day 1 to Day 14.

14.2.2 Sensitivity Analyses of Secondary Endpoint

As a sensitivity analysis, the above MMRM model will also be run without including the baseline average score of ocular discomfort and dryness symptom as a covariate on ITT population with observed data only.

As an additional sensitivity analysis of the secondary efficacy endpoint from Day 1 to Day 14 will also be compared between the two treatment groups using two-sample t-tests and Wilcoxon rank sum tests for each follow-up day on ITT population with observed data only and PP population with observed data only. For the two-sample t-tests, the mean differences of treatment groups, along with two-sided 95% CIs and one-sided p-values, will be reported.

In addition, a sensitivity analysis of the secondary efficacy endpoint from Day 1 to Day 14 will be performed using an ANCOVA model including the baseline average score of ocular discomfort and dryness and treatment group to examine treatment differences at each follow-up day on ITT population with observed data only.

Sensitivity analyses of the secondary efficacy endpoint will also be performed on ITT population with multiple imputation by placebo group-based PMM, ITT population with multiple imputation via randomized treatment-group-based MCMC, ITT population with single imputation by LOCF, and analyses of observed data only using the PP population.

Missing data will be imputed for the two individual symptoms, ocular discomfort and dryness averages. Average symptom scores will then be derived, and changes from baseline will be calculated.

Subject listings will be provided for the secondary efficacy endpoint for all randomized patients.

14.2.3 FIGURES

The LS means from the MMRM analysis of the CFB for the average score of the ocular discomfort and dryness symptoms at the bedtime assessment from the patient daily diary will be displayed graphically in a line chart with 95% CI bars by treatment group across visits.

14.3 Exploratory Efficacy Analyses

The exploratory efficacy variables include the following:

- Fluorescein staining [redacted] by regions: [redacted]
- Lissamine green staining [redacted] by regions: [redacted]
- TFBUT
- Conjunctival redness [redacted]
- Patient daily diary ([redacted] Ocular Discomfort & 4-Symptom Questionnaire) during the dosing period
- OSDI
- [redacted] Ocular Discomfort & 4-Symptom Questionnaire at all [redacted] time points
- [redacted] Ocular Discomfort

All exploratory analyses will be performed on the ITT population with observed data only. For endpoints assessed in each eye separately, analyses will be conducted on the study eye only unless otherwise specified.

Analysis of the CFB to each follow-up visit will use an ANCOVA model adjusted for baseline value with treatment group as the explanatory variable. The LS means for each treatment group and the LS mean differences comparing 0.3% SI-614 with placebo will be presented from the model together with SEs, two-sided 95% CIs, and one-sided p-values.

Two-sample t-test for comparison of the CFB to each follow-up visit between 0.3% SI-614 and placebo for all exploratory efficacy endpoints will also be conducted on ITT population with observed data only.

Wilcoxon rank sum test will also be conducted on ITT population with observed data only.

For each exploratory endpoint that is assessed at [redacted] time points (See Appendix 1 for Schedule of Visits and Measurements), the following ANCOVA models will be produced:

- CFB to time-point-matched follow-up visit (i.e., Baseline, [redacted] to Follow-Up Visit, [redacted] Baseline, [redacted] to Follow-Up Visit, [redacted]; or Baseline, [redacted] to Follow-Up Visit, [redacted]
- Change from [redacted] baseline to [redacted] follow-up visit
- CFB [redacted] to [redacted] change to follow-up visit [redacted] to [redacted] change

For each exploratory endpoint that is assessed at only [redacted] time points (Appendix 1), the following ANCOVA model will be produced:

- CFB to time-point-matched follow-up visit (i.e., Baseline, [redacted] to Follow-Up Visit, [redacted] or Baseline, [redacted] to Follow-Up Visit, [redacted])

Subject listings will be provided for all exploratory endpoint assessments for all randomized patients.

14.3.1 Fluorescein Staining [redacted]

Analyses will be conducted as described in Section 14.3 for each region and sum.

The LS means for the fluorescein staining score CFB to each follow-up visit for each region will be displayed graphically in line charts for each time point comparison (CFB, [redacted] to Follow-up Visit) with SE bars by treatment group based on the ANCOVA analysis of the ITT population with observed data only.

14.3.2 Lissamine Green Staining [redacted]

Analyses will be conducted as described in Section 14.3 for each region and sum.

The LS means for the lissamine green staining score CFB to each follow-up visit for each region will be displayed graphically in line charts for each time point comparison (CFB, [redacted] to Follow-up Visit, [redacted]; Change from Baseline, [redacted] to Follow-Up Visit, [redacted] CFB, [redacted] to Follow-Up Visit, [redacted] and Change from Baseline, [redacted] to Follow-Up Visit, [redacted] with SE bars by treatment group across visits.

14.3.3 Tear Film Break-Up Time

Analyses will be conducted as described in Section 14.3.

The LS means of the TFBUT score CFB to each follow-up visit will be displayed graphically in a line charts for each time point comparison (CFB, [redacted] to Follow-Up Visit, [redacted] Change from Baseline, [redacted] to Follow-Up Visit, [redacted] and Change from Baseline, [redacted] to Follow-Up Visit, [redacted] with SE bars by treatment group across visits.

14.3.4 Conjunctival Redness [redacted]

Analyses will be conducted as described in Section 14.3.

The LS means of the conjunctival redness score CFB to each follow-up visit will be displayed graphically in line charts for each time point comparison (CFB, [redacted] to Follow-Up Visit, [redacted] Change from Baseline, [redacted] to Follow-Up Visit, [redacted] and CFB, [redacted] to Follow-Up Visit, [redacted] with SE bars by treatment group across visits.

14.3.5 Patient Daily Diary

Patient daily diary data will be analyzed for each of the following:

- Daily average
- Morning

- Bedtime

Analyses will be conducted at Week 1, Week 2, Week 4, Week 8, and Week 12 as described in Section 14.3. The weekly average for Daily average will be calculated as the average of the morning and evening assessments for each week and symptom. The weekly average for Morning will be calculated as the average of the morning assessments for each week and symptom. The weekly average for Bedtime will be calculated as the average of the evening assessments for each week and symptom.

14.3.6 Ocular Surface Disease Index (OSDI)

Analyses will be conducted as described in Section 14.3 for total OSDI score, subgroup scores, and each individual question score.

The LS means of the CFB to each follow-up visit for total OSDI, subgroup scores, and each individual question score will be displayed graphically in line charts with SE bars by treatment group across visits.

14.3.7 [redacted] Ocular Discomfort & 4-Symptom Questionnaire

Analyses will be conducted as described in Section 14.3 for each symptom.

The LS means of the CFB to each follow-up visit for each [redacted] Ocular Discomfort & 4-Symptom Questionnaire symptom score will be displayed graphically in line charts with SE bars by treatment group across visits.

14.3.8 [redacted] Ocular Discomfort Scale

For the Pre- and [redacted] time points, analyses will be conducted as described in Section 14.3.

LS means of the CFB to each follow-up visit will be displayed graphically in a line chart with SE bars by treatment group based on the ANCOVA analysis of the ITT population with observed data only.

For the [redacted] analysis, an ANCOVA model will be utilized to compare the CFB (area under the curve) to follow-up visit (area under the curve) between 0.3% SI-614 and placebo.

For the [redacted] analysis, the LS means of the CFB (area under the curve) to follow-up visit (area under the curve) will be displayed graphically in a line chart with SE bars by treatment group for each visit.

15 Safety Analyses

All safety analyses will be conducted using the Safety population.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the patient started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE. The AE reporting period ends upon study exit. Study drug includes the investigational drug under evaluation and any comparator drug, vehicle,

or any other medications required by the protocol given during any stage of the study. All AEs will be coded using MedDRA Version 25.0.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens after the first dose of randomized study treatment.

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to them by the patient. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

The relationship of each AE to the study drug should be determined by the Investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the study drug caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the study drug caused the AE.

An overall summary will be presented that includes the number of events and the number and percentage of patients who experienced at least one TEAE, as well as breakdowns of TEAEs further categorized by ocular and non-ocular, severity, relationship to study drug, seriousness and reasons for seriousness, and the number of patients with TEAEs causing premature treatment discontinuation.

In addition to the overall AE summary, summaries will be provided for the following categories of AEs:

- Ocular and non-ocular TEAEs by SOC and PT
- Ocular and non-ocular TEAEs by SOC, PT, and maximum severity
- Ocular and non-ocular TEAEs by SOC, PT, and strongest relationship
- Ocular and non-ocular TEAEs by SOC, PT, maximum severity, and strongest relationship
- Serious TEAEs by SOC and PT
- TEAEs causing premature treatment discontinuation

Furthermore, separate listings will be generated for all AEs, ocular AEs, non-ocular AEs, and SAEs.

15.2 Best-Corrected Visual Acuity

The observed BCVA and CFB will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics (number of patients [n], mean, SD, median, minimum, and maximum) by visit for each treatment group and for all patients in the Safety population.

A subject listing of BCVA will also be produced.

15.3 Slit-Lamp Biomicroscopy

The results of the examination will be summarized using counts and percentages for each treatment group and for all patients in the Safety population at each visit and time point for each eye (study eye and fellow eye). Percentages will be based on the number of patients in a given treatment group, visit, time point, region, and eye with responses. Abnormal CS is the worst graded response and Normal is the best graded response. Shift tables for the slit-lamp biomicroscopy parameters comparing each follow-up visit to baseline will also be provided.

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

15.4 Pregnancy Test

A urine pregnancy test will be conducted for female patients of childbearing potential at Visit 1 (Day -14) [redacted] Visit 7 (Day 85) [redacted] and may be conducted at unscheduled visits during the study. A patient listing of urine pregnancy test results will be generated.

16 Interim Analyses

No interim analyses are planned.

17 Subgroup Analysis by Two Stratification Factors

Subgroup analysis of the primary efficacy endpoint will be performed in subgroups of each stratification factor using the ITT population with the observed data only. For the five subjects who were mis-randomized, the subgroup assignments will first be based on the strata at randomization and then based on the strata of the correct baseline information. The primary endpoint will be analyzed using an ANCOVA model including baseline values and treatment group as covariates on the ITT population with the observed data only. LS means and their respective SEs will be presented from the ANCOVA model along with their two-sided 95% CIs for each treatment group. LS mean difference comparing 0.3% SI-614 treatment to placebo will be presented from the model with SEs, two-sided 95% CIs, and one-sided p-values.

18 Changes from Protocol-Stated Analyses

The intercurrent events described in the Estimands 1 and 2 in the study protocol is not appropriate for two reasons. The intercurrent events may or may not lead to missing data. The missing data may or may not due to intercurrent events. Missing data are described in the missing data handling section if the missing is not the results of the intercurrent events.

19 References

MJ; Gorst-Rasmussen A;Tarp-Johansen. “Fast Tipping Point Sensitivity Analyses in Clinical Trials with Missing Continuous Outcomes under Multiple Imputation.” *Journal of Biopharmaceutical Statistics*, U.S. National Library of Medicine, https://pubmed.ncbi.nlm.nih.gov/35653556/.

20 Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

On May 27, 2023, it was identified that five subjects were randomized using incorrect stratification data at Visit 2, resulting mis-randomization if the correct strata were used. The SAP was revised before the database lock to specify how the mis-randomized subjects will be handled and the impact of the mis-randomization on the primary endpoint will be assessed. Sensitivity analysis and subgroup analysis of the primary efficacy endpoint were added for assessing the impact of the mis-randomization on the primary efficacy endpoint.

21 Tables

Tables that will be included in the topline delivery are shown in **boldface** font.

If Estimand 1 is used for analysis of the primary efficacy endpoint, then tables with Estimand 2 will not be produced. If Estimand 2 is used for analysis of the primary efficacy endpoint, then tables with Estimand 1 will not be produced. Estimand 1 tables have a letter “a” at the end of the table number, and Estimand 2 tables have a letter “b” at the end of the table number.

Table Number	Title	Population
Table 14.1.1	**Patient Disposition**	**All Screened Patients**
Table 14.1.2.1	**Demographics**	**ITT Population**
Table 14.1.2.2	Demographics	PP Population
Table 14.1.2.3	Demographics	Safety Population
Table 14.1.3.1	**Baseline Disease Characteristics**	**ITT Population**
Table 14.1.3.2	Baseline Disease Characteristics	PP Population
Table 14.1.3.3	Baseline Disease Characteristics	Safety Population
Table 14.1.4.1	Ocular Medical History	ITT Population
Table 14.1.4.2	Non-Ocular Medical History	ITT Population
Table 14.1.5.1	Ocular Concomitant Medications	ITT Population
Table 14.1.5.2	Non-Ocular Concomitant Medications	ITT Population

Table Number	Title	Population
Table 14.1.6	The Rate of Intercurrent Events for Primary Efficacy Endpoint at Day 29 [redacted]	ITT Population
Table 14.2.1.1a	**Summary of Primary Efficacy Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]**	**ITT Population with Estimand 1**
Table 14.2.1.1b	**Summary of Primary Efficacy Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]**	**ITT Population with Estimand 2**
Table 14.2.1.2.1a	**Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]**	**PP Population with Estimand 1**
Table 14.2.1.2.1b	**Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]**	**PP Population with Estimand 2**
Table 14.2.1.2.2	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]	ITT Population with PMM
Table 14.2.1.2.3	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]	PP Population with PMM
Table 14.2.1.2.4	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]	ITT Population with MCMC
Table 14.2.1.2.5	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]	PP Population with MCMC
Table 14.2.1.2.6	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]	ITT Population with LOCF

Table Number	Title	Population
Table 14.2.1.2.7	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]	PP Population with LOCF
Table 14.2.1.2.8	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] - Tipping Point Analysis	ITT Population
Table 14.2.1.2.9	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] - Tipping Point Analysis	PP Population
Table 14.2.1.2.10	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]	ITT Population with Observed Data Only
Table 14.2.1.2.11	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted]	PP Population with Observed Data Only
Table 14.2.1.2.12.1a	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] – ANOVA Model Adjusted for the Stratification Factors Using Randomized Strata	ITT Population with Estimand 1
Table 14.2.1.2.12.2	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] – ANOVA Model Adjusted for the Stratification Factors Using the Correct Strata	ITT Population with Observed Data Only
Table 14.2.1.2.13a	Summary of Sensitivity Analysis for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] – ANOVA Model Adjusted for the Stratification Factors for Randomization	PP Population with Estimand 1

Table Number	Title	Population
Table 14.2.1.3.1a	Summary of Supportive Analyses for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] – Two-Sample t-test and Wilcoxon Rank Sum Test	ITT Population with Estimand 1
Table 14.2.1.3.2a	Summary of Supportive Analyses for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] – Two-Sample t-test and Wilcoxon Rank Sum Test	PP Population with Estimand 1
Table 14.2.1.4a	Summary of Exploratory Comparisons between Treatment Groups at Baseline and Day 29 in Total Corneal Fluorescein Staining [redacted]	ITT Population with Estimand 1
Table 14.2.1.5.1	Subgroup Analysis of Primary Efficacy Endpoint for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] by Stratification Factor 1 – Using Randomized Correct Baseline Data	ITT Population with Observed Data Only
Table 14.2.1.5.2	Subgroup Analysis of Primary Efficacy Endpoint for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] by Stratification Factor 2 – Using Randomized Correct Baseline Data	ITT Population with Observed Data Only
Table 14.2.1.5.3	Subgroup Analysis of Primary Efficacy Endpoint for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] by Stratification Factor 1 – Using Randomized Stratification Data	ITT Population with Observed Data Only
Table 14.2.1.5.4	Subgroup Analysis of Primary Efficacy Endpoint for Change from Baseline [redacted] to Day 29 [redacted] in Total Corneal Fluorescein Staining [redacted] by Stratification Factor 2 – Using Randomized Stratification Data	ITT Population with Observed Data Only

Table Number	Title	Population
Table 14.2.2.1	**Summary of Secondary Efficacy Endpoint Analysis for Change from Baseline in Average Score of Ocular Discomfort and Dryness at Bedtime Assessment from the Patient Daily Diary during Day 1 to Day 14 ([redacted] Ocular Discomfort & 4-Symptom Questionnaire) – MMRM Model**	**ITT Population with Observed Data Only**
Table 14.2.2.2.1	Summary of Sensitivity Analysis for Secondary Efficacy Endpoint –MMRM Model without Baseline Covariate	ITT Population with Observed Data Only
Table 14.2.2.2.2	Summary of Sensitivity Analysis for Secondary Efficacy Endpoint –Two-Sample t-tests, Wilcoxon Rank Sum Tests, and ANCOVA Model	ITT Population with Observed Data Only
Table 14.2.2.2.3	Summary of Sensitivity Analysis for Secondary Efficacy Endpoint	ITT Population with PMM
Table 14.2.2.2.4	Summary of Sensitivity Analysis for Secondary Efficacy Endpoint	ITT Population with MCMC
Table 14.2.2.2.5	Summary of Sensitivity Analysis for Secondary Efficacy Endpoint	ITT Population with LOCF
Table 14.2.2.2.6	Summary of Sensitivity Analysis for Secondary Efficacy Endpoint	PP Population with Observed Data Only
Table 14.2.3.1.1	Summary of Exploratory Efficacy Endpoint Analysis for Change from [redacted] to [redacted] at Each Visit in Fluorescein Staining [redacted]	ITT Population with Observed Data Only
Table 14.2.3.1.2	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted]	ITT Population with Observed Data Only
Table 14.2.3.1.3	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline ([redacted] to [redacted] Change) to Follow-up Visit ([redacted] to [redacted] Change) in Fluorescein Staining [redacted]	ITT Population with Observed Data Only

Table Number	Title	Population
Table 14.2.3.1.4	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline to Time-Point-Matched Follow-up Visit in Fluorescein Staining [redacted]	ITT Population with Observed Data Only
Table 14.2.3.2.1	Summary of Exploratory Efficacy Endpoint Analysis for Change from [redacted] to [redacted] at Each Visit in Lissamine Green Staining [redacted]	ITT Population with Observed Data Only
Table 14.2.3.2.2	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted]	ITT Population with Observed Data Only
Table 14.2.3.2.3	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline ([redacted] to [redacted] Change) to Follow-up Visit ([redacted] to [redacted] Change) in Lissamine Green Staining [redacted]	ITT Population with Observed Data Only
Table 14.2.3.2.4	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline to Time-Point-Matched Follow-up Visit in Lissamine Green Staining [redacted]	ITT Population with Observed Data Only
Table 14.2.3.3.1	Summary of Exploratory Efficacy Endpoint Analysis for Change from [redacted] to [redacted] at Each Visit in Tear Film Break-Up Time (TFBUT)	ITT Population with Observed Data Only
Table 14.2.3.3.2	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline [redacted] to [redacted] Follow-up Visit in Tear Film Break-Up Time (TFBUT)	ITT Population with Observed Data Only
Table 14.2.3.3.3	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline ([redacted] to [redacted] Change) to Follow-up Visit ([redacted] to [redacted] Change) in Tear Film Break-Up Time (TFBUT)	ITT Population with Observed Data Only
Table 14.2.3.3.4	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline to Time-Point-Matched Follow-up Visit in Tear Film Break-Up Time (TFBUT)	ITT Population with Observed Data Only

Table Number	Title	Population
Table 14.2.3.4.1	Summary of Exploratory Efficacy Endpoint Analysis for Change from [redacted] to [redacted] at Each Visit in Conjunctival Redness [redacted]	ITT Population with Observed Data Only
Table 14.2.3.4.2	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline [redacted] to [redacted] Follow-up Visit in Conjunctival Redness [redacted]	ITT Population with Observed Data Only
Table 14.2.3.4.3	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline ([redacted] to [redacted] Change) to Follow-up Visit ([redacted] to [redacted] Change) in Conjunctival Redness [redacted]	ITT Population with Observed Data Only
Table 14.2.3.4.4	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline to Time-Point-Matched Follow-up Visit in Conjunctival Redness [redacted]	ITT Population with Observed Data Only
Table 14.2.3.5.1	Summary of Exploratory Efficacy Endpoint Analysis for Patient Daily Diary ([redacted] Ocular Discomfort & 4-Symptom Questionnaire) – Daily Average	ITT Population with Observed Data Only
Table 14.2.3.5.2	Summary of Exploratory Efficacy Endpoint Analysis for Patient Daily Diary ([redacted] Ocular Discomfort & 4-Symptom Questionnaire) – Morning	ITT Population with Observed Data Only
Table 14.2.3.5.3	Summary of Exploratory Efficacy Endpoint Analysis for Patient Daily Diary ([redacted] Ocular Discomfort & 4-Symptom Questionnaire) – Bedtime	ITT Population with Observed Data Only
Table 14.2.3.6	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Surface Disease Index (OSDI)	ITT Population with Observed Data Only
Table 14.2.3.7	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Discomfort & 4-Symptom Questionnaire [redacted]	ITT Population with Observed Data Only

Table Number	Title	Population
Table 14.2.3.8	Summary of Exploratory Efficacy Endpoint Analysis for Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Discomfort [redacted]	ITT Population with Observed Data Only
Table 14.2.3.9	Summary of Exploratory Efficacy Endpoint Analysis for Ocular Discomfort Scale [redacted]	ITT Population with Observed Data Only
Table 14.3.1.1	**Overall Treatment-Emergent Adverse Events (TEAEs) Summary**	**Safety Population**
Table 14.3.1.2	**Ocular Treatment-Emergent Adverse Events (TEAEs)**	**Safety Population**
Table 14.3.1.3	Non-Ocular Treatment-Emergent Adverse Events (TEAEs)	Safety Population
Table 14.3.1.4	Ocular Treatment-Emergent Adverse Events (TEAEs) by Maximum Severity	Safety Population
Table 14.3.1.5	Non-Ocular Treatment-Emergent Adverse Events (TEAEs) by Maximum Severity	Safety Population
Table 14.3.1.6	Ocular Treatment-Emergent Adverse Events (TEAEs) by Strongest Relationship	Safety Population
Table 14.3.1.7	Non-Ocular Treatment-Emergent Adverse Events (TEAEs) by Strongest Relationship	Safety Population
Table 14.3.1.8	Ocular Treatment-Emergent Adverse Events (TEAEs) by Maximum Severity and Strongest Relationship	Safety Population
Table 14.3.1.9	Non-Ocular Treatment-Emergent Adverse Events (TEAEs) by Maximum Severity and Strongest Relationship	Safety Population
Table 14.3.2	Best-Corrected Visual Acuity (BCVA)	Safety Population
Table 14.3.3.1	Slit-Lamp Biomicroscopy	Safety Population
Table 14.3.3.2	Shift in Slit-Lamp Biomicroscopy	Safety Population
Table 14.4.1	Dosing Compliance	Safety Population
Table 14.4.2	Treatment Exposure	Safety Population

22 Listings

Listing Number	Title	Population
Listing 16.1.7	Randomization Schedule	All Randomized Patients
Listing 16.2.1	Patient Disposition	All Screened Patients
Listing 16.2.2	Protocol Deviations	All Randomized Patients
Listing 16.2.3.1	Analysis Population Inclusion	All Randomized Patients
Listing 16.2.3.2	Inclusion/Exclusion and Screen Failures	All Screened Patients
Listing 16.2.4.1	Demographics	All Randomized Patients
Listing 16.2.4.2.1	Ocular Medical History	All Randomized Patients
Listing 16.2.4.2.2	Non-Ocular Medical History	All Randomized Patients
Listing 16.2.4.3.1	Ocular Prior and Concomitant Medications	All Randomized Patients
Listing 16.2.4.3.2	Non-Ocular Prior and Concomitant Medications	All Randomized Patients
Listing 16.2.4.4.1	Ocular Concomitant Procedures	All Randomized Patients
Listing 16.2.4.4.2	Non-Ocular Concomitant Procedures	All Randomized Patients
Listing 16.2.5.1	Run-In and Study Drug Assignment and Instillation	All Screened Patients
Listing 16.2.5.2	Run-In and Study Drug Accountability	All Screened Patients
Listing 16.2.5.3	Study Drug Exposure and Dosing Compliance	All Randomized Patients
Listing 16.2.6.1	Fluorescein Staining [redacted]	All Randomized Patients
Listing 16.2.6.2	Lissamine Green Staining [redacted]	All Randomized Patients

Listing Number	Title	Population
Listing 16.2.6.3	Tear Film Break-Up Time (TFBUT)	All Randomized Patients
Listing 16.2.6.4	Conjunctival Redness [redacted]	All Randomized Patients
Listing 16.2.6.5	Patient Daily Diary with [redacted] Ocular Discomfort & 4-Symptom Questionnaire	All Randomized Patients
Listing 16.2.6.6	Ocular Surface Disease Index (OSDI)	All Randomized Patients
Listing 16.2.6.7	Ocular Discomfort & 4-Symptom Questionnaire [redacted]	All Randomized Patients
Listing 16.2.6.8	Ocular Discomfort Scale [redacted]	All Randomized Patients
Listing 16.2.6.9	Ocular Discomfort Scale [redacted]	All Randomized Patients
Listing 16.2.7.1	All Adverse Events	All Randomized Patients
Listing 16.2.7.2	Ocular Adverse Events	All Randomized Patients
Listing 16.2.7.3	Non-Ocular Adverse Events	All Randomized Patients
Listing 16.2.7.4	Serious Adverse Events	All Randomized Patients
Listing 16.2.8.1	Best-Corrected Visual Acuity (BCVA)	All Randomized Patients
Listing 16.2.8.2	Slit-Lamp Biomicroscopy	All Randomized Patients
Listing 16.2.8.3	Pregnancy Test Results	All Randomized Female Patients of Childbearing Potential

23 Figures

If Estimand 2 is used for analysis of the primary efficacy endpoint, then Figure 14.1.1.a with Estimand 1 will not be produced. The Estimand 1 figure has a letter “a” at the end of the figure number.

Figure Number	Title	Population
Figure 14.1.1a	Change from Baseline in Total Corneal Fluorescein Staining [redacted] (Mean [± SD] Change from Baseline [redacted]	ITT Population with Estimand 1
Figure 14.2.1	Change from Baseline in Average Score of Ocular Discomfort and Dryness at the Bedtime Assessment from the Patient Daily Diary during Day 1 through Day 14 (LS Means with 95% CI from the MMRM Analysis of Change from Baseline [Day -7 through Day -1])	ITT Population with Observed Data Only
Figure 14.3.1.1	Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.1.2	Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.1.3	Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.1.4	Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.1.5	Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.1.6	Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only

Figure Number	Title	Population
Figure 14.3.1.7	Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.1.8	Change from Baseline [redacted] to [redacted] Follow-up Visit in Fluorescein Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.2.1	Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.2.2	Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.2.3	Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.2.4	Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.2.5	Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.2.6	Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only

Figure Number	Title	Population
Figure 14.3.2.7	Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted] – [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.2.8	Change from Baseline [redacted] to [redacted] Follow-up Visit in Lissamine Green Staining [redacted] - [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.3	Change from Baseline [redacted] to [redacted] Follow-up Visit in Tear Film Break-up Time (TFBUT) (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.4	Change from Baseline [redacted] to [redacted] Follow-up Visit in Conjunctival Redness [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.5	Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Surface Disease Index (OSDI) (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.6.1	Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Discomfort & 4-Symptom Questionnaire [redacted] – Ocular Discomfort (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.6.2	Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Discomfort & 4-Symptom Questionnaire [redacted] – Burning (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.6.3	Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Discomfort & 4-Symptom Questionnaire [redacted] – Dryness (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only

Figure Number	Title	Population
Figure 14.3.6.4	Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Discomfort & 4-Symptom Questionnaire [redacted] – Grittiness (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.6.5	Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Discomfort & 4-Symptom Questionnaire [redacted] – Stinging (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only
Figure 14.3.7	Change from Baseline [redacted] to Time-Point-Matched Follow-up Visit in Ocular Discomfort [redacted] (LS Means [± SE] from ANCOVA Model of Change from Baseline)	ITT Population with Observed Data Only

24 Appendix 1: Schedule of Visits and Measurements

Visit Day	Visit 1 -14±3			Visit 2 1			Visit 3 8±1	Visit 4 15±2			Tel. 22±2	Visit 5 29±3			Tel. 43±2	Visit 6 57±3			Tel. 71±2	Visit 7 85±3		
Placebo Run-in Administration	←	—	→																			
Study Drug Administration							←	—	—	—	—	—	—	—	—	—	—	—	→			
Patient Daily Diary Symptom Assessment								←	—	—	—	—	—	—	—	—	—	—	→			
[redacted]																						
Informed Consent/HIPAA	X																					
Demographics	X																					
Medical/Medication & Ocular History Update	X			X			X	X				X				X				X		
Eligibility Criteria	X		X	X		X																
Urine Pregnancy Test[1]	X																			X		
4-Symptom Questionnaire (in-office)	X			X			X	X				X				X				X		
Ocular Discomfort (in-office)	X	X[2]		X	X[2]		X	X	X[2]			X	X[2]			X	X[2]			X	X[2]	
OSDI	X			X			X	X				X				X				X		
Best-Corrected Visual Acuity	X			X			X	X				X				X				X		X
Slit Lamp Biomicroscopy	X		X	X		X	X	X		X		X		X		X		X		X		X
Conjunctival Redness	X		X	X		X	X	X		X		X		X		X		X		X		X
TFBUT	X		X	X		X	X	X		X		X		X		X		X		X		X
Fluorescein Staining	X		X	X		X	X	X		X		X		X		X		X		X		X
Lissamine Green Staining	X		X	X		X	X	X		X		X		X		X		X		X		X
Run-in Vials Dispensed			X																			
Run-in Instilled (in office)	X		X	X																		
Run-in Vials Collected/Accountability				X																		
Randomization						X																
Study Drug Vials Dispensed						X				X				X				X				
Study Drug Instilled (in office)						X	X	X		X		X		X		X		X		X		
Study Drug Vials Collected/Accountability							X	X				X				X				X		
Daily Diary Dispensed			X			X	X			X				X				X				
Daily Diary Collected				X			X	X				X				X				X		
Adverse Event Query			X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Visit Day	**Visit 1 -14±3**			**Visit 2 1**			**Visit 3 8±1**	**Visit 4 15±2**			**Tel. 22±2**	**Visit 5 29±3**			**Tel. 43±2**	**Visit 6 57±3**			**Tel. 71±2**	**Visit 7 85±3**		
Placebo Run-in Administration	←	—	→																			
Study Drug Administration							←	—	—	—	—	—	—	—	—	—	—	—	→			
Patient Daily Diary Symptom Assessment								←	—	—	—	—	—	—	—	—	—	—	→			
[redacted]																						
Exit from Study																						X

Abbreviations: [redacted] HIPAA. Health Insurance Portability and Accountability Act; OSDI, ocular surface disease index; Tel., Telephone call (to check drug compliance); TFBUT, tear film breakup time

[1]For females of childbearing potential

[redacted]