STATISTICAL ANALYSIS PLAN

A Phase 2, Single-Center, Randomized, Double-Masked, Placebo-Controlled Study to Assess the Safety and Efficacy of IC265 Ophthalmic Solution 1% in Subjects Diagnosed with Dry Eye Disease

Sponsor: IACTA Pharmaceuticals, Inc.
19900 MacArthur Blvd, Suite 550
Irvine, CA 92612

Protocol Number: 23-110-0002

Author: Kay Jackson
Biostatistician
Statistics & Data Corporation

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Statistical Analysis Plan Approval

Prepared by: _____ _____

Kay Jackson — Date
Biostatistician
Statistics & Data Corporation

Reviewed by: _____ _____

Eric Nowicki, PhD — Date
Sr. Director, Biostatistics
Statistics & Data Corporation

Reviewed by: _____ _____

Ahren Velasco — Date
Sr. Biostatistics Quality Control Specialist
Statistics & Data Corporation

Approved by: _____ _____

Eric Carter — Date

Chief Medical Officer

IACTA Pharmaceuticals, Inc.

Approved by: _____ _____

Anoshie Ratnayake — Date

Medical Monitor

IACTA Pharmaceuticals, Inc.

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BID	*Bis in die* (Twice Daily)
CAE	Controlled Adverse Environment
CFB	Change from Baseline
CI	Confidence Interval
CS	Clinically Significant
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NCS	Not Clinically Significant
QD	*Quaque die* (Once Daily)
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RDC	Remote Data Capture
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe in detail the planned analyses and reporting for protocol 23-110-0002, Version 3.0 dated 22AUG2023. 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.

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.

The decision to terminate protocol 23-110-0002 was determined 16NOV2023 due to the emergent adverse events of Epithelial Haziness. Details on how the termination affected the protocol-state analyses can be found in Section 17.

2. Study Objectives

The objective of this study is to compare the safety and efficacy of IC265 Ophthalmic Solution 1% to placebo for the treatment of the signs and symptoms of dry eye disease.

3. Study Endpoints

3.1 Primary Endpoints

As this is an exploratory study, there are no primary endpoints.

3.2 Secondary Endpoints

As this is an exploratory study, there are no secondary endpoints.

3.3 Efficacy Endpoints

The efficacy endpoints include the following:

- Fluorescein staining (Ora Calibra® scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
- Ocular discomfort and dry eye symptoms at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)
- Lissamine green staining (Ora Calibra® scale) at Visits 3, 4 (pre- CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post- CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score

- Tear film break-up time (TFBUT) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post- CAE)
- Conjunctival Redness at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post- CAE), and mean change from baseline Visit 2 (Day 1) pre-CAE to Visit 5 (Day 84) pre-CAE
- Ocular Surface Disease Index (OSDI) at Visits 3, 4, and 5 (pre- CAE)
- Schirmer's test at Visit 3, 4, and 5
- Ocular discomfort during CAE at Visits 4 and 5
- Daily Diary Symptom Score

3.4 Safety Endpoints

The safety endpoints include the following:

- Visual acuity
- Slit-lamp evaluation
- Adverse event query
- Intraocular pressure
- Undilated fundoscopy
- Drop comfort assessment after randomization at Visit 2, 3, 4, and 5

3.5 Statistical Hypotheses

The clinical hypotheses for this study is that IC265 Ophthalmic Solution 1% twice daily (BID) is superior to its vehicle (BID) for the efficacy endpoints.

4. Study Design and Procedures

4.1 General Study Design

This is a Phase 2, single-center, double-masked, randomized, placebo-controlled clinical study. Subjects will be randomized to one of the following treatment arms at Visit 2 (Day 1):

- IC265 Ophthalmic Solution 1%: 1 drop BID bilaterally (N=~20)
- Placebo Ophthalmic Solution (Vehicle): 1 drop BID bilaterally (N=~20)

Approximately 40 subjects will be randomly assigned to one of the two groups (1:1) to receive either IC265 Ophthalmic Solution 1% or placebo solution as topical ophthalmic drops administered bilaterally BID for 12 weeks. Subjects, Sponsor, Contract Research Organization (CRO), and site personnel will be masked to treatment assignment.

During the 14-day study run-in period prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally BID.

During the screening period, two 90-minute exposures to the CAE will be conducted to ascertain eligibility to enter the study at Visit 1 (Day -14 ± 2) and Visit 2 (Day 1). Subjects who qualify after the initial screening visit will enter the run-in phase, where they will self-administer vehicle BID for approximately 14 days. Those who qualify at Visit 2 (Day 1) will be randomized to receive study drug in a double-masked fashion for 84 days. Subjects will self-administer drops BID and will complete Daily diary symptom score assessments as instructed. The CAE exposure will occur at Visit 1 (Day -14 ± 2), Visit 2 (Day 1), Visit 3 (Day 15 ± 2), Visit 4 (Day 43 ± 2), and Visit 5 (Day 85 ± 4), with Pre-CAE, during CAE and Post-CAE assessments of ocular signs and symptoms. Study drug will be discontinued at Visit 5. Subjects will exit from the study at this visit.

Study visits will be referred to in all tables and listings as the scheduled visit name and planned study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule.

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided Appendix 1.

4.3 Study Treatments

IC265 Ophthalmic Solution will be formulated as a sterile, non-preserved solution around pH 6 for topical ophthalmic administration and is intended for clinical use. The study drug will be supplied in blow-fill seal ampoules, which allow for product administration directly to the eye. Each ampoule will contain a nominal volume of 0.27 mL.

The excipients which will be used to manufacture IC265 Ophthalmic Solution will be standard excipients for use in ophthalmic solutions that comply with their respective USP / EP monographs.

The placebo for IC265 Ophthalmic Solution contains all the same excipients used in the active formulation without the API.

5. Sample Size

Approximately 80 subjects will be screened to enroll 40 subjects (20 subjects in each group). This is a Phase 2 study for which no formal sample size calculation has been performed. The sample size chosen was not based on statistical considerations, but is based on historical experience.

6. Data Preparation

6.1 Input Data

Study data will primarily be recorded on the electronic Case Report Forms (eCRFs) supplied by SDC using iMedNet and SDC Capture™.

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 SDC.

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

- Database lock has occurred.
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

6.2 Output Data

Data from EDC will be transferred to SDC Biostatistics. Data will then be mapped to analysis datasets. Both raw and analysis data will be used to create the subject listings, while all tables and figures will be based on the analysis data.

7. Analysis Populations

7.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population includes all randomized subjects. All efficacy analyses will be performed on the ITT Population, and subjects will be analyzed as randomized.

7.2 Safety Population

The Safety Population includes all randomized subjects who receive at least one dose of the investigational product. The subjects will be analyzed as treated. All safety analyses will be based on the Safety Population.

8. General Statistical Considerations

8.1 Unit of Analysis

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

Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with the worst (higher) total corneal fluorescein staining, based on the sum of the inferior, superior, and central regions, at baseline (Visit 2) pre-CAE. If the total corneal staining is the same in both eyes, then the right eye will be selected as the study eye.

The non-study eye will be referred to as the fellow eye. Fellow eye safety summaries will also be presented as appropriate. Additionally, non-ocular AEs and medical history will be presented at the subject level.

8.2 Missing or Inconclusive Data Handling

8.2.1 Missing Efficacy Assessments

No imputation will be used for efficacy endpoints.

8.2.2 MISSING SAFETY ASSESSMENTS

No imputation will be used for safety endpoints.

8.3 Definition of Baseline

Baseline measures are defined as the last non-missing measure prior to the initiation of randomized study treatment, usually at Visit 2 (Day 1).

8.4 Data Analysis Conventions

All data analysis will be performed by SDC. 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), arithmetic mean, standard deviation (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 counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between active treatment and placebo will be calculated as, Active – Placebo, and change from baseline will be calculated as, Follow-up Visit – Baseline.

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit. Listings will be presented by subject number, treatment group, visit, time point, and parameter as applicable based on all randomized subjects unless otherwise specified.

8.5 Adjustments for Multiplicity

As this is an exploratory study with no primary or secondary endpoints, there will be no multiplicity adjustments and all analyses are considered hypothesis-generating.

9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized to masked study drug, with subcategories of dosed with the masked study drug and did not dose with masked study drug; who were included in the ITT and Safety Populations; and who completed the study and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and overall for all subjects. Percentages will be calculated using screened subjects as the denominator unless otherwise specified.

The reasons for premature study discontinuation will be summarized by treatment group and overall for all discontinued subjects. Percentages will be calculated using discontinued subjects as the denominator. The reasons for study discontinuation that will be summarized include: lost to follow-up, adverse event (AE),

protocol violation, administrative reasons, sponsor termination of study, subject request/withdrawal, and other. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

The number and percentage of subjects with any deviation will be summarized by treatment group and overall for all subjects. The protocol deviations that will be summarized include the following categories: non-compliance with informed consent, non-compliance with study inclusion or exclusion criteria, site's non-compliance with study treatment, subject's non-compliance with study treatment, improper protocol procedures at site, site's failure to report serious adverse events (SAE) and/or adverse events (AE), non-compliance with any scheduled study visit, use of disallowed concomitant medications, subject's failure to follow instructions, and other. A subject listing will be provided that includes the date of the deviation, the deviation category, the deviation description, and the classification of whether the deviation was judged to be major or minor in a masked review.

Details of the study randomization, including randomization date, randomized treatment, and actual treatment, will also be included within a subject listing.

10. Demographics and Physical Examination

10.1 Demographic Variables

The demographic variables collected in this study include age, gender assigned at birth (i.e., sex), race, ethnicity, and iris color. Subjects who record more than one race will be grouped into a single category denoted as Multi-racial in the summary table and will be reported as collected in the subject listing. Iris color will be summarized at the subject level. Demographic variables will be summarized for the ITT and Safety Populations, separately.

Age (years) will be summarized, by treatment group and overall for all subjects, using continuous descriptive statistics. Age will be reported in years and calculated using the following formula:

Age (years) = (Informed Consent Date – Date of Birth) / 365.25, truncated as an integer

The number and percentage of subjects will be presented, by treatment group and overall for all subjects, for sex, race, ethnicity, and iris color.

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

10.2 Physical Examination

Physical examinations of general health, head, eye, ear, nose and throat (HEENT), and other body systems will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS).

A subject listing that includes all physical examination results will be provided.

11. Medical History and Concomitant Medications

Listings of medical history, concomitant medications, and concomitant procedures will be generated separately, as well as separately for ocular and non-ocular data.

11.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 26.1.

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group and overall for all subjects at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the Safety Population. Ocular medical history will be similarly summarized at the subject level. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs are ordered in ascending alphabetical order, and PTs within an SOC are sorted by descending frequency for all subjects.

11.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, B3, September 2023 version 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 highest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name.

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

Concomitant medications will be summarized using the ITT Population. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. In the summaries, ATC Classes and preferred names will be presented in ascending alphabetical order. A listing will be provided of prior and concomitant medications.

11.3 Concomitant Procedures

Concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 26. 1. Concomitant procedures will not be summarized, but a listing will be provided.

12. Dosing Compliance and Treatment Exposure

In addition to the analyses described in the following sections, subject listings will be provided for study drug assignment, study drug instillation, and subject daily dosing diary records.

12.1 Dosing Compliance

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

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

The number of actual doses received will be calculated from the number of used vials recorded in the drug accountability eCRF or from the subject diary and in-office instillations. The number of expected doses that will be used for calculating compliance will be calculated as:

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

for all subjects, regardless of study completion status.

A categorical dosing compliance variable will also be derived as non-compliant (< 80%), compliant (≥ 80% and ≤ 125%), and over compliant (> 125%).

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group using the ITT Population. The compliance category defined above will be summarized with discrete summary statistics.

A subject listing of dosing compliance will also be produced.

12.2 Treatment Exposure

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

$$\text{Extent of Exposure (days)} = (\text{Date of Last Dose} - \text{Date of First Dose}) + 1$$

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

$$\text{Extent of Exposure (days)} = (\text{Date of Last Recorded Visit} - \text{Date of First Dose}) + 1$$

Extent of treatment exposure for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group using the Safety Population. A subject listing of treatment exposure will also be produced.

13. Exploratory Efficacy Analyses

13.1 Primary Analysis of Exploratory Efficacy Variables

All efficacy analyses will be conducted using the ITT Population.

13.1.1 Fluorescein Staining (Ora Calibra® Scale)

Fluorescein staining will be conducted at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score.

The staining will be graded with the Ora Calibra® Corneal and Conjunctival Staining Scale, which is as follows: 0 = None, 1 = Trace, 2 = Mild, 3 = Moderate, 4 = Severe. Half (0.5) increments may be used.

The fluorescein staining results for the study eye will be summarized using continuous descriptive statistics by visit and eye for each treatment group and all randomized subjects. A subject listing of fluorescein staining results will also be produced.

13.1.2 Ocular discomfort and dry eye symptoms

Ocular discomfort scores will be subjectively graded by the subjects according to the following scale, rating each eye separately: 0 = No discomfort, 1 = Intermittent awareness, 2 = Constant awareness, 3 = Intermittent discomfort, 4 = Constant discomfort. Additionally, subjects will rate the severity of each of the following symptoms, with regard to how both their eyes feel, in general – overall ocular discomfort, burning, dryness, grittiness and stinging according to the following 6-point (0 to 5) scale where 0 = none and 5 = worst. Both ocular discomfort and dry eye symptoms will be assessed at each visit.

Ocular discomfort and dry eye symptoms for the study eye will be summarized using continuous descriptive statistics by visit for each treatment group and all randomized subjects. A subject listing of ocular discomfort and 4-symptom questionnaire results will also be produced.

13.1.3 Lissamine Green Staining (Ora Calibra® Scale)

Lissamine green staining will be conducted at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score.

The staining will be graded with the Ora Calibra® Corneal and Conjunctival Staining Scale, which is as follows: 0 = None, 1 = Trace, 2 = Mild, 3 = Moderate, 4 = Severe. Half (0.5) increments may be used.

The lissamine staining results for the study eye will be summarized using continuous descriptive statistics by visit and eye for each treatment group and all randomized subjects. A subject listing of lissamine staining results will also be produced.

13.1.4 TEAR FILM BREAK-UP TIME

TFBUT will be measured in seconds using a stopwatch and a digital image recording system for the right eye followed by the left eye at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post- CAE). For each eye, 2 measurements will be taken and averaged unless the 2 measurements are > 2 seconds apart and are each < 10 seconds, in which case, a third measurement would be taken and the 2 closest of the 3 would be averaged.

The TFBUT values for the study eye will be summarized using continuous descriptive statistics by visit and eye for each treatment group and for all randomized subjects. A subject listing of TFBUT will also be produced.

13.1.5 CONJUNCTIVAL REDNESS

The Ora Calibra® Conjunctival Redness Scale for Dry Eye will be performed at Visits 2 (pre-CAE), 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE). The scale is as follows: 0 = None, 1 = Trace, 2 = Mild, 3 = Moderate, 4 = Severe. Half (0.5) increments may be used.

The scale values for the study eye will be summarized using continuous descriptive statistics by visit and eye for each treatment group and all randomized subjects. A subject listing of conjunctival redness results will also be produced.

13.1.6 OCULAR SURFACE DISEASE INDEX (OSDI)

Ocular Surface Disease Index (OSDI©) includes the following questions:

1. Eyes that are sensitive to light?
2. Eyes that feel gritty?
3. Painful or sore eyes?
4. Blurred vision?
5. Poor vision?
6. Reading?
7. Driving at night?
8. Working with a computer or bank machine (ATM)?
9. Watching TV?
10. Windy conditions?
11. Places or areas with low humidity (very dry)?
12. Areas that are air conditioned?

OSDI© will be collected for both eyes at Visits 1, 2, 3, 4 and 5 (pre-CAE). The 5-unit scale for responses to the OSDI© is given by the following: 0 = None of the time, 1 = Some of the time, 2 = Half of the time, 3 = Most of the time, and 4 = All of the time. The total OSDI© score is calculated by the following:

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

Note that the number of questions answered in the denominator should exclude those questions with a response of "N/A." Continuous descriptive statistics, including 95% CIs, as well as changes from baseline will be summarized by treatment group as well as between treatment groups. All categorical safety assessments will be summarized by treatment and time point (as applicable) using discrete summary statistics. A subject listing of OSDI© results will also be produced.

13.1.7 Unanesthetized Schirmer's Test

Subjects' will have the length of the moistened area from the sterile Tear Flo Schirmer strip assessed in each eye at Visits 3, 4, and 5. The Schirmer's test strip will be placed in the lower temporal lid margin of each eye. After 5 minutes, the test strip will be removed, and the length of the moistened area will be recorded in millimeters (mm) for each eye.

The length values for the study eye will be summarized using continuous descriptive statistics by visit and eye for each treatment group and for all actively treated subjects. A subject listing of Schirmer's test results will also be produced.

13.1.8 Ocular Discomfort During CAE

Ocular discomfort scores will be subjectively graded by the subjects according to the following Ora Calibra® Ocular Discomfort Scale for Dry Eye, rating each eye separately, where: 0 = No discomfort, 1 = Intermittent awareness, 2 = Constant awareness, 3 = Intermittent discomfort, 4 = Constant discomfort. The procedure will occur during the 90 minute CAE exposure, starting at time 0 and then every 5 minutes thereafter.

Ocular discomfort scores at Visits 4 and 5 for the study eye will be summarized using continuous descriptive statistics by visit and eye for each treatment group and for all actively treated subjects. A subject listing of ocular discomfort scores will also be produced.

13.1.9 Daily Diary Symptom Score

Subjects will be asked to complete a dosing diary daily between Visit 1 and Visit 5. The diary symptom scores will be summarized using continuous descriptive statistics for each treatment group and for all actively treated subjects, for the following windows: Day -14 to Day 0, Day 1 to Day 7, Day 8 to Day 14, Day 15 to Day 28, Day 29 to Day 42, Day 43 to Day 63, Day 64 to Day 85. A subject listing will be provided for daily dosing diary records.

13.2 Sensitivity Analysis of Efficacy Variable(s)

Sensitivity analyses will not be conducted for efficacy variables.

14. Safety Analyses

All safety analyses will be conducted using the Safety Population.

14.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the first dose of study drug administration. Only TEAEs will be summarized, however all AEs collected in the eCRF will be presented in data listings. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 26.1.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one TEAE, by treatment group. This summary will also include breakdowns of TEAEs further categorized as ocular (study eye and fellow eye separately) or non-ocular, treatment-related TEAEs, treatment-emergent serious adverse events (TE-SAEs), TEAEs leading to early treatment discontinuation, TEAEs leading to death, and TEAEs by maximum severity.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE by treatment group and classified by the MedDRA SOC and PT. Ocular and non-ocular TEAEs will be summarized separately. If a subject reports multiple TEAEs to the same SOC or multiple PTs within the same SOC, the subject will be counted only once within that SOC or PT. In the summaries, SOCs will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Separate summaries by SOC and PT will be provided for the following categories of AEs:

- Ocular TEAEs
- Non-ocular TEAEs
- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs
- TE-SAEs

Summaries of TEAEs by maximum severity will be presented for ocular AEs and non-ocular TEAEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same SOC or PT within an SOC, the subject will be counted once under the maximum severity.

All AEs will be presented in a subject listing. In addition, SAEs and AEs leading to study treatment discontinuation will be listed separately.

14.2 Visual Acuity

The logarithm of the minimum angle of resolution (logMAR) visual acuity is assessed at each visit using an Early Treatment Diabetic Retinography Study (ETDRS) chart. Subjects should use their most recent correction to attain their visual acuity (VA).

The observed and change from baseline visual acuity will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics by visit for each treatment group and for all actively treated subjects. A subject listing of visual acuity will also be produced. This listing will include a variable that indicates if a subject had a visual acuity change from baseline of ≥0.2 on the logMAR scale.

14.3 Slit-Lamp Biomicroscopy

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, and eyelid will be performed at each visit. The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS).

The results will be summarized using counts and percentages for each treatment group and for all actively treated subjects at each visit for each eye (study eye and fellow eye). Percentages will be based on the number of subjects in each treatment group with responses. Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing each follow-up visit to baseline. A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

14.4 Undilated Fundoscopy

An undilated fundoscopy examination of the vitreous, retina, macula, choroid and optic nerve will be performed at each visit. The results will be graded as normal, abnormal NCS, or abnormal CS.

The results will be summarized using counts and percentages for each treatment group and for all actively treated subjects at each visit for each eye (study eye and fellow eye). Percentages will be based on the number of subjects in each treatment group with responses. Shift tables for the undilated fundoscopy parameters will also be provided comparing each follow-up visit to baseline. A subject listing of the undilated fundoscopy parameters will also be produced.

14.5 Intraocular Pressure

Subjects' IOP will be assessed by non-contact tonometry in each eye at each visit. Results will be taken from a single measurement and will be recorded in millimeters of Mercury (mmHg).

The IOP values and changes from baseline for each eye (study eye and fellow eye) will be summarized using continuous descriptive statistics by visit and eye for each treatment group and for all actively treated subjects. A subject listing of IOP will also be produced. This listing will include identifiers which indicates if a subject had an IOP increase from baseline of ≥6 or ≥10 mmHg.

14.6 Drop Comfort Scale Assessment

Subjects' drop comfort will be assessed for each eye at Visits 2, 3, and 4 using the Ora Calibra® Drop Comfort Scale, where 0 indicates Very Comfortable and 10 indicates Very Uncomfortable.

The scale values for each eye (study eye and fellow eye) will be summarized using continuous descriptive statistics by visit and eye for each treatment group and all randomized subjects. A subject listing of drop comfort results will also be produced.

15. Other Data

15.1 Physical Examination

Physical examinations of general health, head, eye, ear, nose and throat (HEENT), and other body systems will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS).

A subject listing that includes all physical examination results will be provided.

15.2 Visual Analog Scale

A VAS instrument measures a characteristic that spans a continuum, cannot be precisely or optimally measured by, or would lack sensitivity in distinguishing subtle changes on an ordinal scale. VAS will be administered to assess the subject's experience of ocular discomfort (unrelated to study drug instillation), where higher score indicates greater discomfort.

A subject listing that includes all VAS results will be provided.

16. Interim Analyses

There will be no interim analyses in this study. To note, the study was terminated early on 16NOV2023.

17. Changes from Protocol-Stated Analyses

Changes from the protocol-stated analyses, due to early termination of the study on 16NOV2023, include the following:

- Per Protocol population will not be determined.
- No imputation will be used for efficacy or safety endpoints. Specifically, the ITT population will not be analyzed using the Last Observation Carried Forward (LOCF) imputation method and multiple imputation.
- Sensitivity analyses will not be conducted as the PP population has been removed and no imputation will be used.
- Statistical testing will not be conducted. Descriptive statistics will be utilized for the efficacy and safety endpoints.

18. References

1. *ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 05 February 1998.
2. *ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports E3*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 30 November 1995.

19. Revision History

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

20. Tables

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

Table Number	Title	Population
14.1.1	**Subject Disposition**	**All Screened Subjects**
14.1.2	Protocol Deviations	Intent-to-Treat Population
14.1.2.1	**Demographics**	**Intent-to-Treat Population**
14.1.2.2	**Demographics**	**Safety Population**
14.1.3.1	Ocular Medical History	Safety Population
14.1.3.2	Non-Ocular Medical History	Safety Population
14.1.4.1	Ocular Concomitant Medications	Intent-to-Treat Population
14.1.4.2	Non-Ocular Concomitant Medications	Intent-to-Treat Population
14.1.5.1	Study Drug Compliance	Intent-to-Treat Population
14.1.5.2	**Overall Study Drug Exposure**	**Safety Population**
14.2.1.1	Ora Calibra Corneal and Conjunctival Fluorescein Staining in Study Eye by Visit	Intent-to-Treat Population
14.2.1.2	**Ora Calibra Ocular Discomfort & 4-Symptoms Questionnaire in Study Eye by Visit**	**Intent-to-Treat Population**

Table Number	Title	Population
14.2.1.3	**Ora Calibra Ocular Discomfort Scale during the CAE in Study Eye by Visit**	**Intent-to-Treat Population**
14.2.1.4	Ora Calibra Corneal and Conjunctival Lissamine Green Staining in Study Eye by Visit	Intent-to-Treat Population
14.2.1.5	Tear Film Break-Up Time (TFBUT) in Study Eye by Visit	Intent-to-Treat Population
14.2.1.6	**Ora Calibra Conjunctival Redness in Study Eye by Visit**	**Intent-to-Treat Population**
14.2.1.7	Ocular Surface Disease Index (OSDI) by Visit	Intent-to-Treat Population
14.2.1.8	Unanesthetized Schirmer's Test in Study Eye by Visit	Intent-to-Treat Population
14.2.1.9	Daily Diary Symptom Score	Intent-to-Treat Population
14.3.1.1	**Overall Summary of Adverse Events**	**Safety Population**
14.3.1.2	**Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**	**Safety Population**
14.3.1.3	**Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**	**Safety Population**
14.3.1.4	**Ocular Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**	**Safety Population**
14.3.1.5	**Non-Ocular Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**	**Safety Population**
14.3.1.6	**Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**	**Safety Population**
14.3.2	Visual Acuity (logMAR) by Visit	Safety Population
14.3.3.1	Slit Lamp Biomicroscopy Results by Visit	Safety Population
14.3.3.2	Shifts in Slit Lamp Biomicroscopy from Baseline to Each Post-Baseline Visit	Safety Population
14.3.4.1	Undilated Fundus Exam Results by Visit	Safety Population
14.3.4.2	Shifts in Undilated Fundus Exam Results from Baseline to Each Post-Baseline Visit	Safety Population

Table Number	Title	Population
14.3.5	Intraocular Pressure by Visit	Safety Population
14.3.6	**Ora Calibra Drop Comfort Scale by Visit**	**Safety Population**

21. Listings

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

Listing Number	Title	Population
16.1.7	Randomization Schedule	All Randomized Subjects
16.2.1.1	**Subject Dispositions**	**All Randomized Subjects**
16.2.1.2	Inclusion/Exclusion Criteria	All Screened Subjects
16.2.2	Protocol Deviations	All Randomized Subjects
16.2.4.1	Demographics	All Randomized Subjects
16.2.4.2	Medical History	All Randomized Subjects
16.2.4.3	Prior and Concomitant Medications	All Randomized Subjects
16.2.4.4	Concomitant Procedures	All Randomized Subjects
16.2.5.1	Study Drug Assignment and Accountability	All Randomized Subjects
16.2.5.2	Study Drug Exposure and Dosing Compliance	All Randomized Subjects
16.2.5.3	Study Drug Instillation	All Randomized Subjects
16.2.6.1	Ora Calibra Corneal and Conjunctival Fluorescein Staining	All Randomized Subjects
16.2.6.2	Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire	All Randomized Subjects
16.2.6.3	Ora Calibra Ocular Discomfort Scale during the CAE	All Randomized Subjects

Listing Number	Title	Population
16.2.6.4	Ora Calibra Corneal and Conjunctival Lissamine Green Staining	All Randomized Subjects
16.2.6.5	Tear Film Break-Up Time (TFBUT)	All Randomized Subjects
16.2.6.6	Ora Calibra Conjunctival Redness	All Randomized Subjects
16.2.6.7	Ocular Surface Disease Index (OSDI)	All Randomized Subjects
16.2.6.8	Unanesthetized Schirmer's Test	All Randomized Subjects
16.2.6.9	Daily Diary Symptom Score	All Randomized Subjects
16.2.7.1	**All Adverse Events**	**All Randomized Subjects**
16.2.7.2	**Serious Adverse Events**	**All Randomized Subjects**
16.2.7.3	**Adverse Events Leading to Study Treatment Discontinuation**	**All Randomized Subjects**
16.2.8.1	Urine Pregnancy Test Results	All Randomized Female Subjects of Childbearing Potential
16.2.9.1	Visual Acuity (VA)	All Randomized Subjects
16.2.9.2	Slit-Lamp Biomicroscopy	All Randomized Subjects
16.2.9.3	Undilated Fundoscopy	All Randomized Subjects
16.2.9.4	Intraocular Pressure (IOP)	All Randomized Subjects
16.2.9.5	Ora Calibra Drop Comfort Scale	All Randomized Subjects
16.2.9.6	Ora Calibra Ocular Discomfort Scale outside the CAE	All Randomized Subjects
16.2.9.7	Physical Examination	All Randomized Subjects

Listing Number	Title	Population
16.2.9.8	Visual Analog Scale (VAS)	All Randomized Subjects

22. Figures

Figure Number	Title	Population

23. Appendices

23.1 Appendix 1: Schedule of Visits and Measurements

Procedure	Visit 1 Day -14 ± 2		Visit 2 Day 1		Day 8 ± 2	Visit 3 Day 15 ± 2		Day 29 ± 2	Visit 4 Day 43 ± 2		Day 64 ± 2	Visit 5 Day 85 ± 4/Early Termination	
	Pre-CAE	Post - CAE	Pre-CAE	Post-CAE	Phone Call	Pre-CAE	Post-CAE	Phone Call	Pre-CAE	Post-CAE	Phone Call	Pre-CAE	Post-CAE
Informed Consent / HIPAA	X												
Medical / Medication History and Demographic	X												
Run-in Collection			X										
Study drug Collection						X			X			X	
Eyecup Phone and/or Diary Collection			X			X			X			X	
Medical / Medication History Update			X			X			X			X	
Adverse Event Query	X		X		X	X		X	X		X	X	
Pregnancy Test	X[1]											X[1]	
Physical Exam (HEENT)			X										
Ora Calibra™ Ocular Discomfort & 4-Symptom Questionnaire	X	X	X	X		X	X		X	X		X	X
OSDI© Questionnaire	X		X			X			X			X	
Visual Analog Scale (VAS)	X		X			X			X			X	
y (Visual Acuity (ETDRS)	X		X			X			X			X	
Review of Qualification Criteria	X	X	X	X									
Slit-lamp Biomicroscopy	X	X	X	X		X	X		X	X		X	X

TFBUT	X	X	X	X		X	X		X	X		X	X
Fluorescein Staining	X	X	X	X		X	X		X	X		X	X
Lissamine Green Staining	X	X	X	X		X	X		X	X		X	X
Conjunctival Redness	X	X	X	X		X	X		X	X		X	X
CAE® Exposure	X		X			X			X			X	
Ora Calibra™ Ocular Discomfort Scale	X[2]		X[2]			X[2]			X[2]			X[2]	
Digital Photography*	X	X	X	X		X	X		X	X		X	X
Unanesthetized Schirmer's Test	X		X			X			X			X	
Intraocular Pressure		X											X
Undilated Fundus Exam		X											X
Run-in Article Dispensation		X											
Run-in Instillation		X											
Randomization				X									
Randomized Study Drug Instillation				X			X			X			
Drop Comfort Assessment				X			X			X			
Study Drug Dispensation				X			X			X			
Eyecup Phone and/or Diary Dispensation		X		X			X			X			
Exit Subject from Study													X

X[1] = For females of childbearing potential, **X**[2] = Procedure started at time 0 and then conducted every 5 minutes thereafter during the 90 minute CAE℠ exposure
* Digital Photography (photos of the eye may be taken during Pre-CAE ocular assessments, CAE exposure, and Post-CAE ocular assessment)