STATISTICAL ANALYSIS PLAN

A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of TOP1630 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Syndrome

Sponsor: TopiVert Pharma Ltd

Protocol Number: TOP1630-TV-04

Author: [redacted]
Sr. Biostatistician
Statistics & Data Corporation

Date: 15 May 2017

Version: Final 1.0

Protocol Title

A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of TOP1630 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Syndrome

Protocol Number: **TOP1630-TV-04**

Version: **Final 1.0**

Date: **15 May 2017**

Statistical Analysis Plan Approval

Prepared by: _____ _____

[redacted]
Sr. Biostatistician
Statistics & Data Corporation

Date

Reviewed by: _____ _____

[redacted]
Sr. Principal Biostatistician
Statistics & Data Corporation

Date

Approved by: _____ _____

[redacted]
Vice President, Dry Eye
Ora, Inc.

Date

Approved by: _____ _____

[redacted]
Chief Medical Officer
TopiVert

Date

Approved by: _____ _____

[redacted]
Head of Clinical Development
TopiVert

Date

Table of Contents

List of Abbreviations

AE	Adverse Event
AICc	Akaike information criterion with a correction for finite sample sizes
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-corrected Visual Acuity
CAE®	Controlled Adverse Environment
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CS	Compound Symmetry
CSR	Clinical Study Report
DDE	Drug Dictionary Enhanced
DES	Dry Eye Syndrome
DHHS	Department of Health and Human Services
DVM	Data Validation Manual
eCRF	Electronic Case Report Form
EKG	Electrocardiograph
ERC	Ethical Review Committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional/independent Review Board
mITT	modified intent-to-treat
IUD	Intra Uterine Device
IWRS	Interactive Web Response System
KCS	Keratoconjunctivitis Sicca
Kg	Kilogram
LASIK	Laser in Situ Keratomileusis
LOCF	Last Observation Carried Forward
LS	Least Squares
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities

MGD	Meibomian Gland Dysfunction
Mg	Milligram
mL	Milliliter
Mm	Millimeter
NEI	National Eye Institute
µg	Microgram
µL	Microliter
µm	Micrometer
mmHg	Millimeters of Mercury
OD	Right Eye
OPI	Ocular Protection Index
OS	Left Eye
OSDI©	Ocular Surface Disease Index
OU	Both Eyes
OTC	Over-the-counter
PMNs	Polymorphonuclear Leucocytes
PP	Per Protocol
PT	Preferred Term
TID	Three Times a Day
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDC	Statistics and Data Corporation
SOC	System Organ Class
SOP	Standard Operating Procedure
TFBUT/TBUT	Tear Film Break-up Time
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
VAS	Visual Analogue Scale
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol TOP1630-TV-04, version 2.0 dated 20Jan2017.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (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 (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the CSR.

2. Study Objectives

The primary objective of this study is to compare the safety and tolerability of TOP1630 Ophthalmic Solution to placebo. The secondary objectives are to compare the efficacy of TOP1630 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye syndrome.

3. Study Variables

3.1 Safety Variables

The safety variables are the following:

- Visual acuity (VA) (ETDRS)
- Slit-lamp biomicroscopy
- Corneal sensitivity [Pre- (Controlled Adverse Environment) CAE®]
- Adverse event (AE) query
- Undilated fundoscopy
- Vital signs at all visits
- Drop comfort assessment
- Intraocular pressure (IOP) (non-contact)

3.2 Exploratory Efficacy Variables

- Corneal fluorescein staining on the Ora Calibra® and National Eye Institute (NEI) scales
- Conjunctival lissamine green staining on the Ora Calibra® and NEI scales
- Visual Analogue Scale (VAS) (Pre-CAE®)
- Tear film break-up time (TFBUT)
- Conjunctival redness the Ora Calibra® scale
- Schirmer Test at Visits 2b, 3b, and 4b
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

- Ocular Surface Disease Index (OSDI©)
- Ora Calibra® Lid Margin Redness
- Ora Calibra® Posterior Lid Edge Evaluation
- Ocular Protection Index (OPI) 2.0
- Ora Calibra® Ocular Discomfort Scale

3.3 Biomarkers

- Impression Cytology (OPIA Eyeprim™).

3.4 Statistical Hypotheses

The null and alternative hypotheses, based on the exploratory efficacy variables, are as follows:

H_0: There is no difference between the TOP1630 Ophthalmic Solution treatment group and placebo for the respective endpoint.

H_1: There is a difference between the TOP1630 Ophthalmic Solution treatment group and placebo for the respective endpoint. A difference in favor of TOP1630 Ophthalmic Solutions will be considered a success for that endpoint.

All hypothesis testing will be two-sided with a type I error rate (α) of 0.10. There will be no adjustments for multiple endpoints or multiple treatment comparisons for this early phase, exploratory study. Specifics of the statistical tests are provided in Section 14.

4. Study Design and Procedures

4.1 General Study Design

This is a Phase 2, single-center, randomized, double-masked, placebo controlled clinical study to assess the safety and tolerability of TOP1630 ophthalmic solution, and the efficacy of TOP1630 ophthalmic solution compared to placebo in subjects with dry eye syndrome. This study consists of two assessments, the Comfort Assessment and the Safety and Efficacy Assessment. The goal of this SAP is to describe the statistical methodologies that will be applied to the Safety and Efficacy Assessment component of the study; therefore, the Comfort Assessment is not included.

For the Safety and Efficacy Assessment, approximately 150 subjects will be screened to enroll approximately 60 randomized subjects. The Safety and Efficacy Assessment will consist of two periods: a 7-day run-in period, during which subjects will instill placebo Ophthalmic Solution (Vehicle) bilaterally TID and a 28-day treatment period, during which subjects will instill randomized study medication TID in both eyes. Subjects will be randomized in a 1:1 ratio (30 subjects in the TOP1630 arm and 30 in the placebo arm) with 4 visits over the course of approximately 5 weeks (including 1 week run-in).

At Visit 1b (Day -7 ±1), Subjects will be challenged for 90 minutes in the CAE® model and will be assessed for eligibility. At Visit 2b (Day 1), subjects will be reassessed for eligibility, re-challenged for 90 minutes in the CAE® model and have baseline measures assessed. Eligible subjects will be randomized to receive either active drug (TOP1630) or placebo (in the ratio of 1 active: 1 placebo).. Randomized subjects will then begin using study drug bilaterally TID for approximately 4 weeks. At Visit 3b (Day 15 ± 1) and Visit 4b (Day 29 ± 2), subjects will be challenged for 90 minutes in the CAE® model.

Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. The following tables show the scheduled study visits, their planned study day, and the acceptable visit window for each study visit for the Comfort Assessment and the Safety and Efficacy Assessment.

For Comfort Assessment:

Scheduled Visit	Planned Study Day	Visit Window
Visit 1a	Day 1	N/A
Visit 2a	Day 2	N/A
Visit 3a	Day 3	N/A
Visit 4a	Day 4	N/A
Visit 5a	Day 5	N/A
Visit 6a	Day 6	N/A
Visit 7a	Day 8	N/A
Visit 8a	Day 12	N/A

For Safety and Efficacy Assessment:

Scheduled Visit	Planned Study Day	Visit Window
Visit 1b	Day -7	± 1
Visit 2b	Day 1	-
Visit 3b	Day 15	± 1
Visit 4b	Day 29	± 2

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments for the Safety and Efficacy Assessment:

Procedure	Visit 1b Day -7 ± 1		Visit 2b Day 1		Visit 3b Day15 ± 1		Visit 4b Day 29 ±2	
	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®
Informed Consent / HIPAA	X							
Medical / Medication History and Demographic	X							
Run-in Placebo Collection			X					
Study Drug Collection					X		X	
Diary Collection			X		X		X	
Medical / Medication History Update			X		X		X	
Adverse Event Query	X	X	X	X	X	X	X	X
Pregnancy Test	X[1]						X[1]	
Ocular Discomfort – Ora, Calibra® / Dry Eye Symptoms	X	X	X	X	X	X	X	X
OSDI© Questionnaire	X		X		X		X	
Visual Acuity (ETDRS)	X		X		X		X	
Vital Signs	X		X		X		X	
Review of Qualification Criteria	X	X	X	X				
Slit-lamp Biomicroscopy	X	X	X	X	X	X	X	X
VAS Symptom Assessment	X		X		X		X	
Impression Cytology (EyePrim)				X				X
Conjunctival Redness, Ora Calibra® Scale	X	X	X	X	X	X	X	X
Lid Margin Redness, Ora Calibra® Scale	X		X		X		X	
Posterior Lid Edge Evaluation, Ora Calibra® Scale	X		X		X		X	
TFBUT	X	X	X	X	X	X	X	X
Fluorescein Staining-Ora Calibra® and NEI Scale	X	X	X	X	X	X	X	X
Lissamine Green Staining-Ora Calibra® and NEI Scale	X	X	X	X	X	X	X	X
Corneal Sensitivity (Cochet-Bonnet)	X						X	
OPI 2.0			X				X	
Unanesthetized Schirmer's Test	X		X		X		X	
CAE® Exposure	X		X		X		X	
CAE® Discomfort – Ora Calibra® Ocular Discomfort Scale	X		X		X		X	
Intraocular pressure (non-contact)		X						X
Undilated Fundus Exam		X						X

Run-in Placebo & Diary Dispensation		X						
Randomization				X				
Subject self-instillation of study drug				X		X		
Ora Calibra® Drop Comfort Assessment				X		X		
Study Drug Dispensation				X		X		
Diary Dispensation		X		X		X		
Exit Subject from Study								X
[1]For females of childbearing potential.								

5. Study Treatments

The investigational treatment for this study is TOP1630 Ophthalmic Solution. The control is Placebo Ophthalmic Solution (Vehicle with no TOP1630).

5.1 Method of Assigning Subjects to Treatment Groups

Prior to initiation of study run-in (at Visit 1b), each subject who qualifies for entry will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. If all inclusion and exclusion criteria are met at Visits 1b and 2b, each qualifying subject will then be assigned a randomization number at the end of Visit 2b. Subjects who meets all qualification criteria will be randomly assigned to masked treatment using a 1:1 (approximately 30 subjects in the TOP1630 arm and approximately 30 in the placebo arm) assignment ratio. Subjects will be randomized by assignment of the next 4-digit randomization number available (3001-3100). No randomization numbers will be skipped or omitted. An independent randomization specialist who is not otherwise involved in the trial will generate the randomization code utilized at site. The unique randomization list will assign masked study kit numbers to be dispensed to each enrolled subject. At the end of Visit 1b, qualified subjects will receive a kit of run-in (Placebo) for one week, dosing TID until Visit 2b. At the end of Visit 2b and 3b, subjects will be given two kits of 24 bottles each of TOP1630 Ophthalmic Solution or placebo for TID dosing. At Visits 3b and 4b, remaining/unused study drug will be collected from subjects for drug accountability.

5.2 Masking and Unmasking

This is a double-masked study. Subjects, investigators and site staff, the sponsor and Ora/Statistics & Data Corporation (SDC) staff are masked to the treatment group assignments during the randomization process and for the duration of the study.

Under normal circumstances, the mask should not be broken. When medically necessary, an investigator may need to determine what treatment has been assigned to a subject. The investigator will contact Ora/Sponsor with the details of the emergency unmasking request. Ora/Sponsor will make the final determination if the unmasking request will be granted. If granted, the investigator will complete unmasking via the “scratch-off” label affixed to the subject’s source documents. If the unmasking label is not available, unmasking information may be provided by the Unmasked designees [redacted]). The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Subjects should have their study drug discontinued immediately if treatment assignment is unmasked.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data have been entered into the database, data queries have been resolved, and assignment of subjects to the analysis populations has been completed. The database will be kept masked until after the database lock has occurred.

6. Sample Size and Power Considerations

The study is not powered to show statistical differences for any of the efficacy endpoints. The sample size was determined based on prior clinical trial experience in subjects with dry eye syndrome and is deemed to be robust sufficient to evaluate the safety and tolerability of TOP1630 Ophthalmic Solution in this population and to gather efficacy data that will aid in powering future clinical trials.

With a sample size of 60 subjects in the Safety and Efficacy Assessment, the study will have 79% probability of detecting AEs occurring at a rate of 5% or more in either treatment arm.

7. Data Preparation

Data management procedures, including database design, selection of the data dictionary, and coding of all AEs and medications, will be performed by SDC. All reported study data will be recorded on the electronic Case Report Forms (eCRF) supplied by SDC using [redacted] Clinical personnel at the study center and Ora, Inc. are responsible for ensuring that the protocol is followed and that the eCRFs are properly completed.

After data are entered into the clinical study database, electronic edit checks will be performed, including checks for missing data, out of range values, discrepancies within and across visits, and cross checks between different data tables. All data validation specifications and procedures are detailed in the Data Validation Manual (DVM). When the database has been declared to be complete and accurate, the database will be locked and treatment codes unmasked. Any changes to the database after that time can only be made with the approval of the Sponsor in consultation with Ora, Inc. and SDC.

All analyses outlined in this document will be performed after:

- All data management requirements are met according to SDC's Standard Operating Procedures (SOP), including performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Ora/Sponsor personnel;
- All protocol deviations have been classified as major or minor and the Per Protocol population has been determined; and
- The treatment codes have been unmasked.

8. Analysis Populations

8.1 Modified Intent-to-Treat

The modified Intent-to-Treat (mITT) population includes all randomized subjects with one post baseline efficacy assessment. Efficacy analysis will be performed on the mITT population. Subjects in the mITT population will be analyzed as randomized.

8.2 Per Protocol

The PP population includes subjects in the mITT population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed and determined prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.

8.3 Safety

The Safety population includes all subjects who have received at least one dose of the investigational product. The Safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

Summaries of the comfort data from the Comfort Assessment will be performed on the Safety population from that Assessment. The statistical analysis of safety data will be performed for the Safety population, separately for the Comfort Assessment and the Safety and Efficacy Assessment. The analysis of baseline and all efficacy data in the Safety and Efficacy Assessment will be performed for the mITT population. The efficacy analyses may also be performed on the PP population as sensitivity analyses.

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 “worst eye” as defined by the following:

Worst 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 worse (higher) increase in total corneal staining change from pre-CAE® to post-CAE® at Visit 2b on the Ora Calibra® scale. If the increase in total corneal staining is the same in both eyes, then the study eye will be the eye with the largest increase in ocular discomfort from pre-CAE® to post-CAE® at Visit 2b. If the ocular discomfort symptom increase is the same in both eyes, then the right eye will be selected as the worst eye.

9.2 Missing or Inconclusive Data Handling

The efficacy analyses will be performed using observed data. In addition, for key endpoints of corneal staining and ocular discomfort, missing data will be imputed using the following methods:

- Using the last observation carried forward (LOCF) imputation method for missing values
- Using multiple imputation methods to account for missing data

9.3 Definition of Baseline

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 2b. If a measure is taken both pre-CAE® and post-CAE®, the baseline will be the time point matched value at Visit 2b. For measures from daily subject diaries, baseline is defined as the average of all available days' readings during the run-in period, where daily scores are first obtained by averaging the AM and PM scores for that day, as applicable. For changes from pre-CAE® to post-CAE® post first treatment, the change from pre-CAE® to post-CAE® at Visit 2b will be considered the baseline value. For purposes of analysis, only subjects with at least 5 days of data in the run-in period will be included in change from baseline summaries and analyses.

9.4 Data Analysis Conventions

All data analysis will be performed by SDC 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.

Quantitative variables will be summarized using descriptive statistics including the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum values. Means, medians, and confidence intervals (CI) will be reported to two decimal places and SDs to three. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between the active treatment group and placebo will be calculated as Active minus Placebo and change from baseline will be calculated as follow-up visit minus baseline.

All efficacy analyses will be 2-sided at a significance level of 0.10. CIs for differences between treatment groups will be two-sided at 90% confidence. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999".

All summaries will be presented by treatment group. Summaries of data from the Comfort Assessment and Safety and Efficacy Assessment of the study will be summarized separately. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

For the purpose of summarization, the following will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug Dictionary Enhanced (DDE), as appropriate: medical history, concurrent therapies, and AEs.

9.5 Adjustments for Multiplicity

There will be no adjustments for multiple endpoints or multiple treatment comparisons for this early phase, exploratory study.

10. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, 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 for all subjects.

The number and percentage of subjects discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all randomized subjects. The reasons for study discontinuation that will be summarized include: AEs, protocol violations, administrative reasons, sponsor termination of study, subject choice, 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 protocol deviations will be summarized by treatment group for all randomized subjects. A subject listing will be provided that includes the date of the deviation, the deviation description and the classification of whether the deviation was judged to be major or minor.

In addition, subject listings will be provided that include informed consent date, inclusion and exclusion criteria violations, and exclusions from the PP population.

11. Demographic and Baseline Variables

11.1 Demographic Variables

The demographic variables collected in this study include age, gender, race, ethnicity and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years. Age will be reported in years and calculated using the following formula:

Age = (informed consent date – date of birth) / 365.25 truncated as an integer

The number and percentage of subjects will be presented, overall and by treatment, for age category, gender, race, ethnicity and iris color. Percentages will be based on the total number of subjects in each treatment group except for iris color, which will be based on the total number of eyes in each treatment group. A subject listing that includes all demographic variables will be provided.

11.2 Baseline Variables

Baseline worst dry eye symptoms, duration of dry eye syndrome and OSDI© will be summarized and listed.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by system organ class (SOC) and preferred term (PT). 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, then that SOC will only be reported once. Separate tables will be created for ocular and non-ocular medical history. Medical history will be coded using MedDRA, version 20.0. The summaries will be based on the mITT population.

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

12.2 Prior and Concomitant Medications

At the first screening visit, subjects will be asked what medications they are taking, as well as those the subject may have taken prior to Visit 1b. At each study visit, subjects will be asked what concomitant medications they are currently taking or if there have been any changes to their medication since their first visit.

All prior and concomitant ocular and non-ocular medications will be listed using the mITT population including generic name, route of administration, start date, stop date, dosage, and indication. Prior and concomitant medications will be coded using the WHO DDE version B2, September 2016, to the appropriate Anatomical Therapeutic Chemical (ATC) classification and WHO generic term.

Counts and percentages of ocular and non-ocular concomitant medications will be summarized separately using WHO Drug ATC classification and preferred name. Summaries will be displayed by treatment group and for all subjects. Subjects with multiple medications in the same ATC class or preferred name will be counted only once for that respective ATC class or preferred name.

13. Dosing Compliance and Treatment Exposure

13.1 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:

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

$$\frac{\text{Number of Expected Doses}}{} \times 100\%$$

The number of actual doses received will be calculated from the used and unused bottles recorded in the eCRF. The number of expected doses that will be used for calculating compliance will be calculated as {3x [date of last dose – date of Visit 2 (Day 1)]} +3 for all subjects, regardless of study completion status.

A categorical dosing compliance variable will also be derived as non-compliant (<80%), compliant (≥80% and ≤114%) and over compliant (>114%).

Treatment compliance (%) will be summarized for the Safety population using continuous descriptive statistics. The compliance categories defined above will be summarized with counts and percentages.

A subject listing of compliance will also be produced.

13.2 Treatment Exposure

For the Safety and Efficacy Assessment, extent of exposure will be calculated in days using the following:

Extent of Exposure (days) = [Date of last dose – Date of Visit 2b (Day 1)] + 1

Extent of treatment exposure (days) 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.

14. Safety Analyses

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by SOC and PT; by SOC, PT and maximal severity; by SOC and PT for treatment-related AEs; by SOC, PT for SAEs; and by SOC, PT, and time of onset. Separate summaries will be provided for ocular specific and all AEs (including systemic).

Other safety endpoints including VA, slit-lamp biomicroscopy, corneal sensitivity, undilated fundoscopy, IOP (non-contact), and vital signs will be summarized by treatment group, visit, and time point (where relevant) using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized.

Safety variables will be summarized as appropriate. All safety analyses will be performed on the Safety population. No statistical inferential testing will be performed for safety variables.

14.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an investigational product (IP) in humans, whether or not considered IP-related. TEAEs are defined as AEs that occur after the first use of IP. Per the protocol, only AEs that begin or worsen after receipt of the first dose of IP will be captured in the database for this study; therefore, TEAEs and AEs are equivalent in this study and will be denoted as AEs. All AEs will be assigned a severity grade of mild, moderate, or severe. Their relationship to IP will be classified as suspected (definite, probable or possible) or not suspected (not related). The expectedness of an AE will be classified as unexpected, expected or not applicable. Documentation of AEs will include onset date, severity, action(s) taken, IP relationship, expectedness, outcome, resolution date, and seriousness. All AEs will be coded using MedDRA classifications with reference to SOCs and PTs (MedDRA version 20.0).

An adverse event is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

An overall tabular summary of AEs will be presented that includes the number of events and the number and percentage of subjects who experienced at least one event, by treatment group and overall. This summary will also include breakdowns of AEs further categorized as ocular or non-ocular, SAEs, AEs by maximal severity, AEs leading to subject withdrawal and AEs resulting in death. Additional summaries of AEs will be provided showing the number and percentage of subjects who experienced at least one AE, separately for ocular and non-ocular AEs. Ocular and non-ocular AEs will be summarized separately using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT using the Safety population. 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. The occurrence of AEs suspected to be related to IP will also be tabulated by SOC and PT, separately for ocular and non-ocular events. SAEs will also be summarized separately for ocular and non-ocular events. All AEs will be presented in a listing.

14.2 Visual Acuity (ETDRS)

VA will be measured at the beginning of every study visit. VA (logMAR) will be summarized at each visit using quantitative summary statistics for both eyes combined by treatment. Qualitative summaries for worsening of acuity of 10 letters or greater from the previous visit will also be tabulated. VA results will be presented in a data listing.

14.3 Slit-Lamp Biomicroscopy Examination

Slit-lamp biomicroscopy examinations will be conducted on both eyes at all scheduled visits, Pre- and Post-CAE®. The slit lamp findings will include examinations of the cornea, conjunctiva, anterior chamber, iris, lens and lid. Each parameter will be graded as normal or abnormal. Abnormal findings will be further classified as not clinically significant (NCS) or clinically significant (CS).

Slit lamp findings will be summarized by treatment group and visit, for the worst eye and fellow eye separately, using qualitative summary statistics (frequency counts and percentages). Percentages will be based on the number of subjects with non-missing values for the treatment group at a given visit.

A shift table will show changes from baseline (Visit 2b (Day 1), Pre-CAE®) to all observations at later study visits and time points. The data for slit lamp biomicroscopy will be presented in a listing.

14.4 Corneal Sensitivity (Cochet-Bonnet)

Corneal Sensitivity will be performed at Visits 1b (Day -7 ± 1) Pre CAE® and 4b (Day 29 ± 2) Pre CAE®. Corneal sensitivity will be summarized for both eyes combined by visit and treatment group using quantitative summary statistics. Results will be listed for both eyes at each visit.

14.5 Undilated Fundoscopy

Undilated fundoscopy examinations will be conducted on both eyes at Visit 1b (Day -7 ± 1) Post-CAE® and Visit 4b (Day 29 ± 2) Post-CAE®. The fundus pathology findings will include examinations of the vitreous, retina, macula, choroid, and optic nerve, and be recorded as normal, abnormal (NCS), or abnormal (CS). Summaries of undilated fundoscopy findings will be presented by treatment and visit, for the worst eye and fellow eye separately, using frequency counts and percentages. Percentages will be based on the number of subjects with non-missing values for the treatment group at a given visit.

A shift table will show changes from baseline (Visit 1b (Day -7 ± 1), Post-CAE® to Visit 4b (Day 29 ± 2), Post-CAE®) on the above variables. The data for undilated fundoscopy will be presented in a listing.

14.6 Intraocular Pressure (IOP)

IOP will be measured at Visits 1b (post-CAE®) and 4b (post-CAE®). IOP will be summarized for both eyes combined by visit and treatment group using quantitative summary statistics. At Visit 4b, an IOP of ≥21 mmHg AND ≥10 mmHg over baseline (Visit 1b) will be considered an AE, and presented in the tabular summary. Results will be listed for both eyes at each visit.

15. Tolerability Analyses

Two tools will be used to assess drop comfort, each of which will be assessed at Visit 2b (Day 1) and Visit 3b (Day 15 ± 1), following the first dose of study drug.

[redacted]

subject will be used for this analysis. Drop comfort will be summarized using quantitative summary statistics. Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis.

- Ora Calibra® Drop Comfort Questionnaire will be used to assess drop comfort [redacted]

Drop Comfort Questionnaire responses will be summarized using qualitative summary statistics. Subjects with at least one negative response will also be summarized.

16. Exploratory Efficacy Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, SD, median, minimum and maximum), and analyzed with two-sample *t*-tests comparing the active treatment groups to placebo. All visit-based data will be analyzed at each visit as well as change from baseline. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline will also be assessed where appropriate. Corneal fluorescein staining by region and total (Ora and NEI scales), lissamine green staining by region, TFBUT, conjunctival redness, unanesthetized Schirmer's test, ocular symptoms (Ora Calibra® scales and VAS), OSDI©, ocular discomfort and changes from baseline in these measures will be analyzed by visit and time point, where applicable (i.e., pre- and post-

CAE®), using two-sample *t*-tests and Wilcoxon rank sum tests. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values. For the measures of symptoms during CAE®, the ANCOVA models will also include the pre-CAE® measure as a covariate. Symptoms recorded on the daily diary will be analyzed using repeated measure ANCOVA models, where baseline scores are calculated as the average scores in the run-in period and post-baseline scores are calculated as weekly morning, afternoon, evening, and daily averages.

The efficacy analyses will be performed using observed data. In addition, for key endpoints of corneal fluorescein staining using the Ora Calibra scale and ocular discomfort, missing data will be imputed using LOCF and multiple imputation methods to assess robustness of the results. The PP population with observed data will also be analyzed as an additional sensitivity analysis.

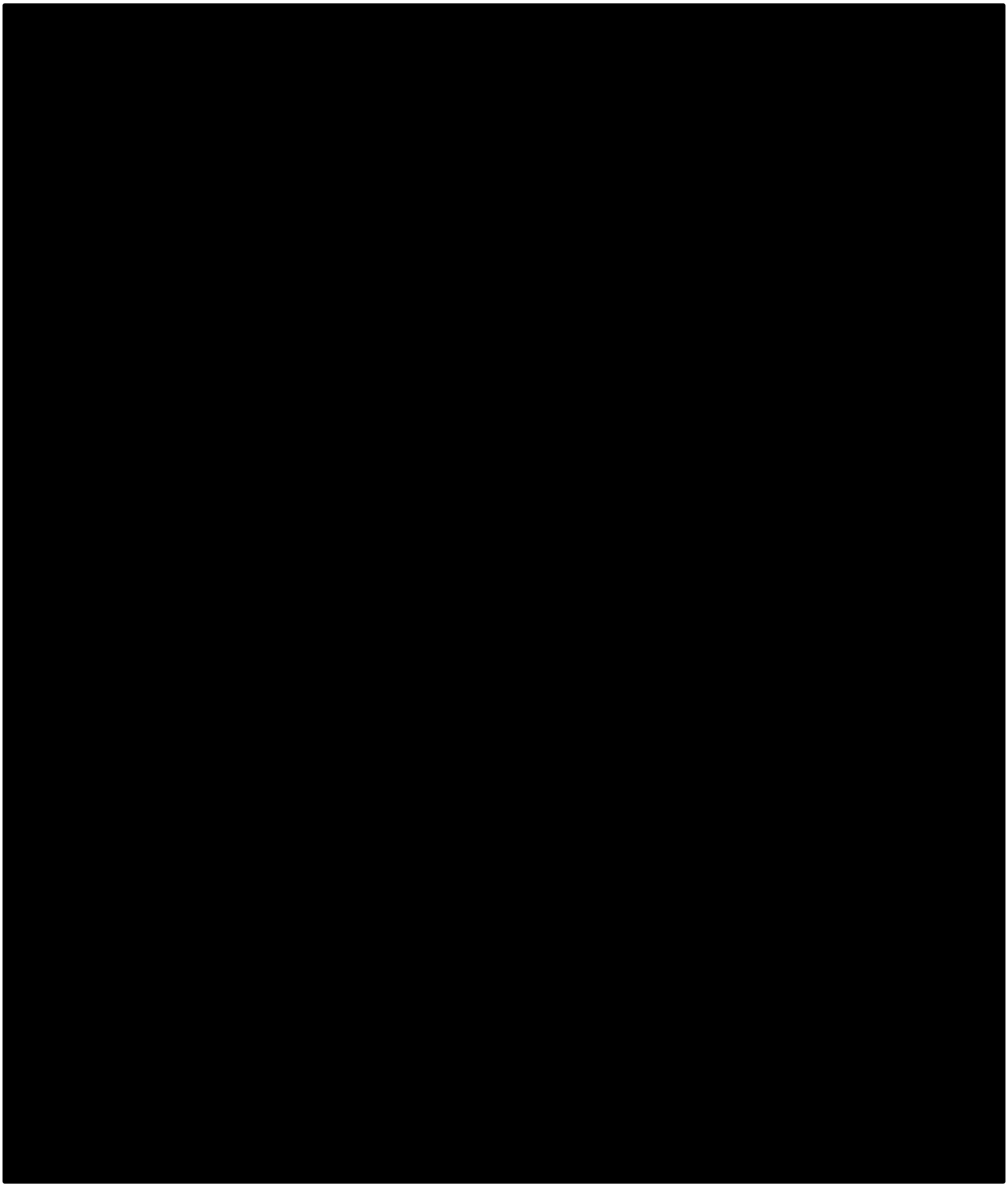
Adjustments for multiplicity will not be employed in this exploratory Phase 2 study.

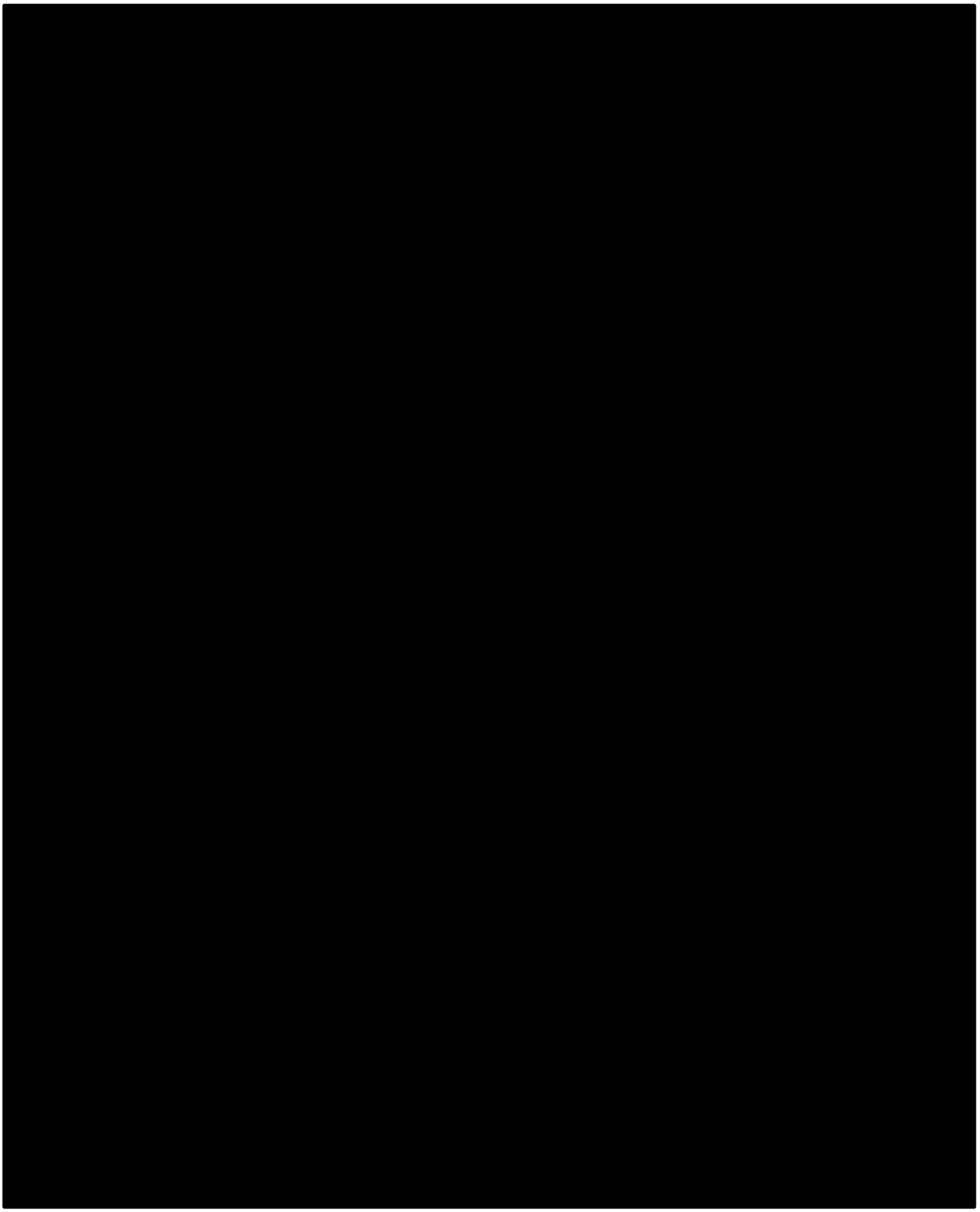
16.1 Corneal Fluorescein Staining

Corneal fluorescein staining (Ora Calibra® and NEI scales) will be performed pre-CAE® and post-CAE® for both eyes at Visit 1b (Day -7 ± 1), Visit 2b (Day 1, prior to treatment), Visit 3b (Day 15 ± 1) and Visit

An analysis of covariance (ANCOVA) model will also be used to compare the changes from baseline for corneal fluorescein staining in each region, as well as the corneal, conjunctival and total staining scores, as measured on the Ora Calibra® and NEI scales, between TOP1630 Ophthalmic Solution and Placebo.

The ANCOVA model will include terms for treatment as the main effect and baseline corneal fluorescein staining as a covariate.





[redacted]

16.2 Ocular Discomfort

Ocular discomfort will be assessed pre-CAE® and post-CAE® for both eyes at Visit 1b (Day -7 ± 1),

[redacted]

Ocular discomfort will be analyzed by visit and time point, where applicable (i.e., pre- and post-CAE® as well as the pre- to post-CAE change), using two-sample t-tests and Wilcoxon rank sum tests.

Change from baseline for ocular discomfort will be analyzed similarly to the change from baseline for corneal fluorescein staining. An ANCOVA model will be used to compare the change from baseline for ocular discomfort, as measured on the Ora Calibra® Ocular Discomfort scale, between TOP1630 Ophthalmic Solution and Placebo. The ANCOVA model will include treatment as the main effect term and baseline ocular discomfort at Day 1 (Visit 2b) as a covariate.

16.3 Lissamine Green Staining

Lissamine green staining will be graded with the Ora Calibra® and NEI scales. The Ora Calibra® Scale

[redacted]

[redacted]

16.4 Tear Film Break-Up Time

TFBUT will be measured in seconds at all scheduled visits, pre- and post-CAE®, on both eyes. For each eye, two measurements will be taken and averaged unless the two measurements are >2 seconds apart and are each <10 seconds, in which case, a third measurement would 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. The worst eye from each subject will be used for this analysis.

TFBUT will be summarized by visit and time point (pre- and post-CAE®) for the mITT Population using quantitative summary statistics. Change from pre- to post-CAE® within each visit as well as change from baseline will also be summarized.

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values.

16.5 Conjunctival Redness

[redacted]

Conjunctival redness will be summarized for the mITT Population with observed data by visit and time point (pre- and post-CAE®) using quantitative summary statistics. Change from pre- to post-CAE® within each visit as well as change from baseline will also be summarized.

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values.

16.6 Lid Margin Redness

Lid margin redness will be assessed at all scheduled visits, pre-CAE®, on both eyes. The grading will [redacted]

Lid margin redness will be summarized for the mITT Population with observed data by visit using quantitative summary statistics. Change from baseline will also be summarized.

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values.

16.7 Posterior Lid Edge Evaluation

Posterior Lid Edge Evaluation will be assessed at all scheduled visits, pre-CAE®, on both eyes. The [redacted]

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values.

16.8 Unanesthetized Schirmer's Test

Unanesthetized Schirmer's Test will be assessed on both eyes at all scheduled visits only at pre-CAE®. 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. Lower values indicate less tears produced in the eye. The worst eye from each subject will be used for this analysis.

Unanesthetized Schirmer's Test will be summarized for the mITT Population with observed data by visit using quantitative summary statistics. Change from baseline will be also summarized.

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values.

16.9 Ocular Surface Disease Index® (OSDI®)

[redacted]

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis.

16.10 Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire

[redacted]

Ocular discomfort and dry eye symptoms will be summarized for the mITT Population with observed data by visit and time point (pre- and post-CAE®) using quantitative summary statistics. Change from pre- to post-CAE® within each visit as well as change from baseline will be also summarized.

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values.

16.11 Ocular Symptoms of Dry Eye Syndrome – Visual Analog Scale (VAS)

Ocular symptoms of dry eye syndrome will be assessed at all scheduled visits, pre-CAE® at the subject level in regard to how both eyes feel. The ocular symptoms of dry eye syndrome visual analog scale will be used, which includes rating of the severity of 7 symptoms: burning/stinging, itching, foreign body sensation, blurred vision, eye dryness, photophobia and pain. Each symptom is rated on a visual analog scale that ranges from 0 to 100 millimeters.

Ocular symptoms of dry eye syndrome will be summarized for the mITT Population with observed data by visit using quantitative summary statistics. Change from baseline will be also summarized.

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values.

16.12 Ocular Discomfort Using the Ora Calibra® Scale

[redacted]

16.12.1 Ora Calibra® Ocular Discomfort Scale Pre-and Post- CAE®

Ocular discomfort scores will be summarized for the mITT Population with observed data by visit and time point using quantitative summary statistics. Change from pre- to post-CAE® within each visit as well as change from baseline will also be summarized.

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis.

16.12.2 Ora Calibra® Ocular Discomfort Scale during CAE®

[redacted]

[redacted]

16.13 Ocular Protection Index (OPI) 2.0

Ocular protection index (OPI) will be assessed at Visits 2b and 4b, Pre-CAE®, on both eyes using the

[redacted]

The OPI and IBI will be summarized by visit using quantitative summary statistics. Change from baseline will also be summarized.

Statistical comparisons will employ two-sample *t*-tests as the primary method of analysis. An ANCOVA model adjusting for baseline will also be assessed as a sensitivity analysis.

16.14 Daily Diary

Each day during the at-home dosing period (including the run-in period), subjects will grade the severity of their dry eye symptoms in their diary in the morning, afternoon and evening prior to each dose. Subjects will rate the severity of each of the following symptoms, with regard to how both their eyes feel:

The individual symptoms will be analyzed using a two-sample *t*-test to compare the two treatment groups. This analysis will be completed separately for the morning, afternoon and evening scores as well as the daily average score. Additionally, the average score for each time point (morning, afternoon, evening and daily average) will also be analyzed separately using a Wilcoxon rank sum test and an ANCOVA model adjusting for baseline, where baseline scores are calculated as the average scores in the run-in period and post-baseline scores are calculated as weekly morning, afternoon, evening, and daily averages.

17. Interim Analyses

No interim analyses are planned for this study.

18. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

19. References

Not applicable

20. Revision History

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

21. 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 Randomized Subjects**
14.1.2.1	**Demographics**	**mITT Population**
14.1.2.2	Demographics	PP Population

Table Number	Title	Population
14.1.3	Baseline Characteristics	mITT Population
14.1.4.1	Ocular Medical History	mITT Population
14.1.4.2	Non-Ocular Medical History	mITT Population
14.1.5.1	Ocular Concomitant Medications	mITT Population
14.1.5.2	Non-Ocular Concomitant Medications	mITT Population
Exploratory Efficacy Analyses		
14.2.1.1	**Corneal Fluorescein Staining (Ora Calibra® Scale)**	**mITT Population**
14.2.1.2	Corneal Fluorescein Staining (Ora Calibra® Scale)	mITT Population with LOCF
14.2.1.3	Corneal Fluorescein Staining (Ora Calibra® Scale)	mITT Population with MCMC
14.2.1.4	Corneal Fluorescein Staining (Ora Calibra® Scale)	PP Population
14.2.2	Corneal Fluorescein Staining (NEI Scale)	mITT Population
14.2.3.1	**Ocular Discomfort**	**mITT Population**
14.2.3.2	Ocular Discomfort	mITT Population with LOCF
14.2.3.3	Ocular Discomfort	mITT Population with MCMC
14.2.3.4	Ocular Discomfort	PP Population
14.2.4	Lissamine Green Staining (Ora Calibra® Scale)	mITT Population
14.2.5	Lissamine Green Staining (NEI Scale)	mITT Population
14.2.6	Tear Film Break-up Time (TFBUT)	mITT Population
14.2.7	Conjunctival Redness	mITT Population
14.2.8	Lid Margin Redness	mITT Population
14.2.9	Posterior Lid Edge Evaluation	mITT Population
14.2.10	Unanesthetized Schirmer's Test	mITT Population
14.2.11	Ora Calibra® Drop Comfort Scale	mITT Population
14.2.12	Ora Calibra® Drop Comfort Questionnaire	mITT Population
14.2.13	Ocular Surface Disease Index (Pre-CAE®)	mITT Population
14.2.14	Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire	mITT Population
14.2.15	Ocular Symptoms – Visual Analog Scale (VAS)	mITT Population
14.2.16	Ora Calibra® Ocular Discomfort Scale during CAE®	mITT Population
14.2.17	Diary Assessments	mITT Population
14.2.18	Ocular Protection Index (OPI) 2.0	mITT Population
Safety Analyses		
14.3.1.1	**Overall Adverse Event Summary**	**Safety Population**
14.3.1.2	**All Ocular Adverse Events**	**Safety Population**
14.3.1.3	**All Non-Ocular Adverse Events**	**Safety Population**
14.3.1.4	All Ocular Adverse Events Suspected to be Related to Investigational Product	Safety Population
14.3.1.5	All Non-Ocular Adverse Events Suspected to be Related to Investigational Product	Safety Population
14.3.1.6	All Ocular Serious Adverse Events	Safety Population
14.3.1.7	All Non-Ocular Serious Adverse Events	Safety Population
14.3.2	Visual Acuity (logMAR)	Safety Population
14.3.3.1	Slit Lamp Biomicroscopy	Safety Population
14.3.3.2	Slit Lamp Biomicroscopy – Shift Table	Safety Population
14.3.4	Intraocular Pressure (mmHg)	Safety Population
14.3.5.1	Undilated Fundoscopy	Safety Population
14.3.5.2	Undilated Fundoscopy – Shift Table	Safety Population
14.3.6	Corneal Sensitivity (Cochet-Bonnet)	Safety Population

Table Number	Title	Population
14.3.7	Compliance with Study Drug	mITT Population
14.3.8	Exposure to Study Drug	mITT Population
14.3.9	Vital Signs	Safety Population

22. Listings

Listing Number	Title	POPULATION
16.1.7	Randomization Schedule	All Randomized Subjects
16.2.1	Subject Disposition	All Randomized Subjects
16.2.2.1	Protocol Deviations	All Randomized Subjects
16.2.2.2	Inclusion and Exclusion Criteria	All Randomized Subjects
16.2.3	Subjects Excluded from the Per Protocol Population	All Randomized Subjects
16.2.4.1	Demographics	All Randomized Subjects
16.2.4.2	Baseline Characteristics	All Randomized Subjects
16.2.4.3	Ocular Medical History	All Randomized Subjects
16.2.4.4	Non-Ocular Medical History	All Randomized Subjects
16.2.4.5	Prior and Concomitant Ocular Medications	All Randomized Subjects
16.2.4.6	Prior and Concomitant Non-Ocular Medications	All Randomized Subjects
16.2.5.1	In-Office Study Medication Instillation	All Randomized Subjects
16.2.5.2	At-Home Study Medication Instillation (Diary)	All Randomized Subjects
16.2.5.3	Study Drug Exposure and Dosing Compliance	All Randomized Subjects
16.2.6.1.1	Corneal fluorescein staining (Ora Calibra® Scale)	All Randomized Subjects
16.2.6.1.2	Corneal fluorescein staining (NEI Scale)	All Randomized Subjects
16.2.6.2	Ocular Discomfort	All Randomized Subjects
16.2.6.3.1	Lissamine Green Staining (Ora Calibra® Scale)	All Randomized Subjects
16.2.6.3.2	Lissamine Green Staining (NEI Scale)	All Randomized Subjects
16.2.6.4	Tear Film Break-up Time (TFBUT)	All Randomized Subjects
16.2.6.5	Conjunctival Redness	All Randomized Subjects
16.2.6.6	Unanesthetized Schirmer's Test (Post-CAE)	All Randomized Subjects
16.2.6.7.1	Ora Calibra® Drop Comfort Scale	All Randomized Subjects
16.2.6.7.2	Ora Calibra® Drop Comfort Questionnaire	All Randomized Subjects
16.2.6.8	Ocular Surface Disease Index (OSDI, Pre-CAE®)	All Randomized Subjects
16.2.6.9.1	Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire	All Randomized Subjects
16.2.6.9.2	Ocular Symptoms of Dry Eye Syndrome – Visual Analog Scale (VAS)	All Randomized Subjects
16.2.6.10	Ora Calibra® Ocular Discomfort Scale During CAE® Exposure	All Randomized Subjects
16.2.6.11	Diary Assessments	All Randomized Subjects
16.2.6.12	Lid Margin Redness (Pre-CAE®)	All Randomized Subjects
16.2.6.13	Posterior Lid Edge Evaluation (Pre-CAE®)	All Randomized Subjects
16.2.6.14	Ocular Protection Index (OPI) 2.0 (Pre-CAE®)	All Randomized Subjects
16.2.6.15	Impression Cytology (OPIA Eyeprim™)	All Randomized Subjects
16.2.7.1	All Adverse Events	Safety Population
16.2.7.2	Serious Adverse Events	Safety Population
16.2.7.3	Adverse Events Leading to Treatment Discontinuation	Safety Population
16.2.7.4	Deaths	Safety Population
16.2.8.1	Visual Acuity (logMAR)	Safety Population
16.2.8.2	Slit Lamp Biomicroscopy	Safety Population
16.2.8.3	Intraocular Pressure (Post-CAE)	Safety Population

Listing Number	Title	POPULATION
16.2.8.4	Undilated Fundoscopy (Post-CAE)	Safety Population
16.2.8.5	Corneal Sensitivity (Cochet-Bonnet) (Pre-CAE)	Safety Population
16.2.8.6	Urine Pregnancy Test Results	Safety Population
16.2.8.7	Vital Signs	Safety Population

23. Figures

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

Figure Number	Figure Title	Population
Figure 14.2.3.1	**Total Corneal Fluorescein Staining as Measured by the Ora Calibra® Scale at Each Visit - Worst Eye (Pre-CAE® to Post-CAE® Change)**	**mITT Population**
Figure 14.2.3.2	Total Corneal Fluorescein Staining as Measured by the Ora Calibra® Scale at Each Visit - Worst Eye (Pre-CAE® to Post-CAE® Change from Baseline)	mITT Population
Figure 14.2.3.3	**Ocular Discomfort as Measured by the Ora Calibra® Scale at Each Visit (Pre-CAE® to Post-CAE® Change)**	**mITT Population**
Figure 14.2.3.4	Ocular Discomfort as Measured by the Ora Calibra® Scale at Each Visit (Pre-CAE® to Post-CAE® Change from Baseline)	mITT Population
Figure 14.2.3.5	Ocular Symptoms of Dry Eye Syndrome – Visual Analog Scale (VAS) at Each Visit (Change from Baseline Pre-CAE®)	mITT Population
Figure 14.2.3.6	Corneal Fluorescein Staining (NEI Scale) at Each Visit (Change from Baseline Pre-CAE®)	mITT Population
Figure 14.2.3.7	Lissamine Green Staining (NEI Scale)at Each Visit (Change from Baseline Pre-CAE®)	mITT Population