STATISTICAL ANALYSIS PLAN

A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye

Sponsor: HanAll Biopharma, Co., Ltd.

Protocol Number: HL036-DED-US-P301

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Version: 2.0

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Statistical Analysis Plan Approval

Prepared by: [redacted] 17 Dec 2019

Date

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Reviewed by: [redacted] 17 Dec 2019

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Approved by: [redacted] 12/17/2019

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Ora, Inc.

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Date

Director, Product and Business Development

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Table of Contents

List of Abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
BID	Bis in die (Twice Daily)
CAE	Controlled Adverse Environment
CI	Confidence Interval
CRF	Case Report Form
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
IP	Investigational Product
IRT	Interactive Response Technlogy
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
NCS	Not Clinically Significant
OD	Oculus Dexter (Right Eye)
OS	Oculus Sinister (Left Eye)
OSDI	Ocular Surface Disease Index
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation, Incorporated
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Treatment-Emergent Serious Adverse Event
TFBUT	Tear Film Break-Up Time
VA	Visual Acuity

VAS	Visual Analog 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 HL036-DED-US-P301, dated 24JAN2019.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

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

2. Study Objectives

The objective of this study is to compare the safety and efficacy of 0.25% HL036 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.

2.1 Primary Variables

The primary efficacy variables of the study are:

- Inferior corneal fluorescein staining (sign);
  and
- Ocular discomfort (symptom).

2.2 Secondary Variables

The secondary efficacy variables include the following:

- Fluorescein staining by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total staining
- Conjunctival lissamine green staining by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total staining
- Conjunctival redness
- Unanesthetized Schirmer's Test
- Tear film break-up time (TFBUT)
- Ocular Surface Disease Index© (OSDI©)

- Visual Analogue Score (VAS)
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Daily symptom diary (Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score)
- Ora Calibra® Drop Comfort Assessment

2.3 Safety Variables

The safety variables include the following:

- Adverse event (AE) query
- Visual acuity
- Slit-lamp evaluation
- Dilated fundoscopy
- Intraocular pressure (IOP)
- Immunogenicity to HL036 in serum

2.4 Statistical Hypotheses

The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided. The primary endpoints will be tested in a hierarchical fixed sequence in the following order.

H_{01}: There is no difference between 0.25% HL036 Ophthalmic Solution and placebo in the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Visit 6 (Day 57 ± 3), using the Ora Calibra® scale.

H_{11}: The change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Visit 6 (Day 57 ± 3) using the Ora Calibra® scale is less with 0.25% HL036 Ophthalmic Solution than with placebo.

H_{02}: There is no difference between 0.25% HL036 Ophthalmic Solution and placebo in the change from baseline of the pre-CAE® ocular discomfort evaluated at Visit 6 (Day 57 ± 3), using the Ora Calibra® Ocular Discomfort Scale.

H_{12}: The change from baseline of the pre-CAE® ocular discomfort at Visit 6 (Day 57 ± 3) using the Ora Calibra® Ocular Discomfort Scale is less with 0.25% HL036 Ophthalmic Solution than with placebo.

3. Study Design and Procedures

3.1 General Study Design

This is a Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel-arm design with block enrollment. Subjects will be randomized to one of the following treatment arms at Visit 2 (Day 1) and will be instructed to follow a twice daily (BID) dosing regimen:

- 0.25% HL036 Ophthalmic Solution (N~315)
- Placebo Solution (N~315)

Approximately 630 subjects will be randomly assigned to one of two treatment groups (1:1) to receive either 0.25% HL036 Ophthalmic Solution or placebo solution as topical ophthalmic drops administered bilaterally BID.

Subjects, Sponsor, Clinical Research Organization, and site personnel will be masked to treatment assignment.

During the screening period, two [redacted] exposures to the CAE® will be conducted to ascertain eligibility to enter the study. Those who qualify will be randomized to receive study drug in a double-masked fashion for 56 days. Subjects will self-administer drops BID and will complete daily symptom diary assessments as instructed.

At Visits 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3), CAE® exposure will occur, with pre-CAE®, during CAE® (symptoms only), and post-CAE® assessments of ocular signs and symptoms. At Visit 3 (Day 8 ± 1) only, no CAE® exposure will occur but signs and symptoms will be assessed.

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

Table 1. Scheduled Study Visits, Planned Study Days, and Visit Windows

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -14	± 1 Day
Visit 2	Day 1	N/A
Visit 3	Day 8	± 1 Day
Visit 4	Day 15	± 2 Days
Visit 5	Day 29	± 2 Days
Visit 6	Day 57	± 3 Days

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided on Table 2.

Table 2. Schedule of Visits and Assessments

Procedure	Visit 1 Day -14 ± 1		Visit 2 Day 1		Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 2		Visit 5 Day 29 ± 2		Visit 6 Day 57 ± 3	
	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Non CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®
Informed Consent / HIPAA	X										
Medical / Medication History and Demographics	X										
Medical / Medication Update			X		X	X		X		X	
Placebo Run-In Dispensation		X									
Placebo Run-in Collection			X								
Randomization				X							
Run-in Instillation		X									
Study Drug Dispensation				X	X[1]		X		X		
Study Drug Instillation				X	X						
Study Drug Collection					X	X		X		X	
Diary Dispensation		X		X	X		X		X		
Diary Collection			X		X	X		X		X	
Review of Qualification Criteria	X	X	X	X							
Adverse Event Query	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X[2]									X[2]	
Drop Comfort Assessment				X							
Ora Calibra® Ocular Discomfort Scale	X	X	X	X	X	X	X	X	X	X	X
Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire	X	X	X	X	X	X	X	X	X	X	X
VAS Discomfort Scale	X	X	X	X	X	X	X	X	X	X	X
OSDI© Questionnaire	X		X		X	X		X		X	
Visual Acuity (ETDRS)	X		X		X	X		X		X	
Slit-lamp Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X
Conjunctival Redness	X	X	X	X	X	X	X	X	X	X	X
TFBUT	X	X	X	X	X	X	X	X	X	X	X
Fluorescein Staining	X	X	X	X	X	X	X	X	X	X	X
Lissamine Green Staining	X	X	X	X	X	X	X	X	X	X	X
CAE® Exposure	X		X			X		X		X	

Procedure	Visit 1 Day -14 ± 1		Visit 2 Day 1		Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 2		Visit 5 Day 29 ± 2		Visit 6 Day 57 ± 3	
	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Non CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®
Discomfort Grading during CAE® Exposure	X		X			X		X		X	
Schirmer's Test		X		X			X		X		X
Intraocular Pressure		X									X
Dilated Fundus Exam		X									X
Blood sampling for Immunogenicity testing				X					X		X
Exit Subject from Study											X[3]

[1] The Visit 2 (Day 1) study drug kit is redispensed at Visit 3 (Day 8 ± 1).
[2] To women of child-bearing potential, as defined.
[3] For subjects with negative immunogenicity results at previous visits (Visits 2, 5, or 6)

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

Prior to initiation of study run-in at Visit 1 (Day -14 ± 1), 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 criteria are met and none of the exclusion criteria are met at Visits 1 (Day -14 ± 1) and 2 (Day 1), each qualifying subject will then be assigned a randomization number at the end of Visit 2 (Day 1) using the Interactive Response Technlogy (IRT) Randomization electronic Case Report Form (eCRF) and will be assigned to 0.25% HL036 ophthalmic solution or placebo solution.

The randomization number will be recorded on the Patient Record Page and eCRF. A new kit will be dispensed at Visits 2 (Day 1) and 4 (Day 15 ± 2) and 5 (Day 29 ± 2) based on the subject's randomization. The Visit 2 (Day 1) kit will be re-dispensed at Visit 3 (Day 8 ± 1). At Visit 5 (Day 29 ± 2), subjects will receive two assigned study drug kits with sufficient supply to last until Visit 6. The Sponsor, investigators, and study staff will be masked during the randomization process and throughout the study.

4.2 Masking and Unmasking

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking study drug. The unmasked subject will be discontinued from the study. Investigators will be able to request emergency unmasking of the treatment through the IRT Randomization eCRF after filling out the Reason for Emergency Unblind Form. 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.

5. Sample Size and Power Considerations

The primary objective of the study is to demonstrate a statistically significant difference between the active treatment and placebo.

This study is expected to enroll 315 subjects in each of the two treatment arms, for a total of 630 randomized subjects. Assuming a 10% drop out rate, 283 subjects per group are expected to complete the study.

Assuming a common standard deviation (SD) in the change from baseline for the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining of 0.74 units, a sample size of 283 subjects per group will have 99% power to detect a difference of 0.3 units between the active treatment group and the placebo group at a two-sided significance level of 0.05. A sample size of 283 subjects per treatment arm will have 93% power to detect a mean difference of 0.3 units in the change from baseline for the pre-CAE® ocular discomfort as assessed by the Ora Calibra® Ocular Discomfort Scale, assuming a SD of 1.03 units. The power for both the sign and symptom endpoints is 93%, assuming independence between the endpoints.

6. Data Preparation

All reported study data will be recorded on the eCRFs supplied by Statistics & Data Corporation, Incorporated (SDC) using iMedNet™ v1.183.4 or higher. Data from source documents will be entered into the eCRF by site personnel.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of HanAll and Ora in consultation with SDC.

All analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to SDC standard operating procedures (SOP), including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC, HanAll and Ora personnel;
- Protocol deviations have been identified and status defined (major/minor deviations);
- Analysis populations have been determined; and
- Randomized treatment codes have been unmasked.

7. Analysis Populations

Analysis populations will include the intent-to-treat (ITT) population, the per-protocol (PP) population, and the Safety population. Analysis will be performed on primary efficacy, baseline, and secondary efficacy data

for the ITT population. Safety data analyses will be performed on the Safety population. The primary efficacy analyses will also be performed on the PP population as sensitivity analyses.

7.1 Intent-to-Treat

The ITT population includes all randomized subjects. The primary analysis will be performed on the ITT population with the Markov Chain Monte Carlo (MCMC) imputation method for missing values. The ITT population may also be analyzed with Last Observation Carried Forward (LOCF) imputation, imputation via pattern mixture models, and with observed data only to assess sensitivity. All efficacy analyses will be performed on the ITT population and subjects will be analyzed as randomized.

7.2 Per Protocol

The PP population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.

7.3 Safety

The Safety population includes all randomized subjects who have received at least one dose of the IP. The Safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

8. General Statistical Considerations

8.1 Unit of Analysis

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

Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with worse (higher) inferior corneal staining pre-CAE® at Visit 2 (Day 1). If the inferior corneal staining is the same in both eyes, then the study eye will be the eye with the highest ocular discomfort pre-CAE® at Visit 2 (Day 1). If the ocular discomfort is the same in both eyes, then the right eye will be selected as the study eye.

8.2 Missing or Inconclusive Data Handling

The primary efficacy analyses will be performed using the Markov Chain Monte Carlo (MCMC) multiple imputation method for missing values. Additionally, last observation carried forward (LOCF) imputation methodology and imputation via pattern mixture models will also be used to impute missing data for the analyses of the primary efficacy variables. For LOCF, the last value from the previous visits will be carried forward, matching pre-CAE® or post-CAE® time points. A pre-CAE® time point will never be imputed for a

post-CAE® value, and vice versa. An analysis using observed data only will also be performed for the primary efficacy variables.

No missing secondary efficacy endpoints or safety endpoints will be imputed.

8.3 Definition of Baseline

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 2 (Day 1). If a measure is taken both pre-CAE® and post-CAE®, the baseline will be the time point matched value at Visit 2 (Day 1). For measures from daily subject diaries, baseline is defined as the average of all days during the run-in period. For changes from pre-CAE® to post-CAE® after the first treatment, the change from pre-CAE® to post-CAE® at Visit 2 (Day 1) will be considered the baseline value.

8.4 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 or higher. Output will be provided in RTF (rich text format) for tables and PDF (portable document format) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all enrolled subjects unless otherwise specified.

All summaries will be presented by treatment group and visit where appropriate, unless otherwise specified. Listings will be presented for all data collected on the eCRFs, sorted by subject id number and visit.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, SD, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence levels where appropriate. 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.”

For statistical analyses that use site as a fixed effect, any site that enrolls fewer than 10 subjects will be pooled with the site with the next smallest enrollment until each pooled site contains at least 10 subjects.

8.5 Adjustments for Multiplicity

Hierarchical fixed sequence testing will be used to maintain the type I error rate for the primary endpoints. The primary analysis will first test the difference in the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Visit 6 (Day 57 ± 3). If the test of the difference is statistically

significant at the two-sided alpha = 0.05 level in favor of HL036, then the study will be considered a success, HL036 will be declared to be superior to placebo in the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Visit 6 (Day 57 ± 3), and the difference in the change from baseline of the pre-CAE® ocular discomfort at Visit 6 (Day 57 ± 3) will be tested at the two-sided alpha = 0.05 level.

If, in addition to a statistically significant test of the difference in change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Visit 6 (Day 57 ± 3) in favor of HL036, the test of the difference in the change from baseline of the pre-CAE® ocular discomfort at Visit 6 (Day 57 ± 3) is also statistically significant in favor of HL036, then HL036 will be declared superior to placebo in both the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining and the change from baseline of the pre-CAE® ocular discomfort at Visit 6 (Day 57 ± 3).

There will be no type I error control procedures for secondary endpoints; therefore, all secondary endpoints will be considered hypothesis generating and no hypothesis testing will be performed.

9. Disposition of Subjects

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

The number of randomized subjects in each of the analysis populations (ITT, PP, and Safety) will be displayed by treatment. The ITT population uses treatment as randomized; PP and Safety populations use treatment as treated. Percentages are based on the total number of subjects randomized in each treatment group.

The number and percentage of subjects prematurely 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: AE, unmasking when medically necessary, protocol violation, administrative reasons (e.g., inability to continue, lost to follow up), 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 any, major, and minor protocol deviations will be summarized by treatment group for all randomized subjects. Major protocol deviations are defined as protocol deviations that may impact primary efficacy endpoints; other protocol deviations are classified as minor. Protocol deviations will be assessed prior to database lock and unmasking. The number and percentage of subjects with any protocol deviation will also be summarized for the following categories: Informed Consent, Inclusion / Exclusion and Randomization, Test Article / Study Drug Instillation and Assignment at Site,

Improper Protocol Procedures at Site, Site's Failure to Report Serious Adverse Event (SAE) / AE, Visit Out of Window, Subject's Non-compliance with Test Article, Subject's Use of Prohibited Concomitant Medication, Subject's Failure to Follow Instructions, and Other. A subject listing will be provided that includes the date, code, description of each deviation and the classification of whether the deviation was judged to be major or minor.

In addition, subject listings will be provided that include randomized and actual treatment, whether inclusion and exclusion criteria were met, and inclusion in the ITT, Safety, and PP populations.

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

The demographic variables collected in this study include age, sex, race, ethnicity, and iris color. Demographic variables will be summarized for the ITT and Safety populations separately.

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, sex, race, ethnicity, and iris OD and OS.

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

10.2 Pretreatment Variables

Baseline disease characteristics will be summarized by treatment group using continuous descriptive statistics for pre-CAE® inferior fluorescein staining, post-CAE® inferior fluorescein staining, pre-CAE® to post-CAE® change in inferior fluorescein staining, pre-CAE® Ora Calibra® Ocular Discomfort Scale, total OSDI© score, best-corrected visual acuity (BCVA), unanesthetized Schirmer's test, and IOP. All summaries will be for the study eye, except for OSDI© which is an OU assessment. The scale for each assessment is provided in the variables' respective subsections in Section 13 of this SAP.

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history will be coded using MedDRA Version 20.1.

Non-ocular 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) using the ITT 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.

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

11.2 Prior and Concomitant Medications

Ocular and non-ocular prior and concomitant medications will be coded using WHODrug Global B3 (September 2017) and coded to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and 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 reported medications that have been taken prior to initiation of study drug administration.

Concomitant medications will be summarized using the ITT population. Prior medications will not be included in data summaries, but will provided on data listings. Concomitant medications will be tabulated for each treatment group and for all subjects using frequencies and percentages. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant and prior medications will be generated separately for ocular and non-ocular data.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Subjects will be instructed on proper completion of the subject daily symptom diary and proper instillation and storage of study drug at the end of Visits 1 (Day -14 ± 1), 2 (Day 1), 3 (Day 8 ± 1), 4 (15 ± 2) , and 5 (Day 29 ± 2) and given written instructions. The subject daily diaries and unused study drug vials will be collected at each visit from Visit 2 (Day 1) up to and including Visit 6 (Day 57 ± 3) to assess dosing and symptom assessment compliance. Dosing compliance will be based off of the unused vial count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of unused vials, then the subject will be deemed non-compliant and a deviation should be recorded.

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

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

The number of doses taken will be calculated by subtracting the number of unused vials from the number of vials dispensed from the electronic case report form (eCRF). For subjects that do not receive a dose of study drug per in office instillation or diary, the number of expected doses will be 0 and compliance will be defined as 0. Otherwise, the number of expected doses will be calculated as 2 x [Date of Last Dose – Date of Visit 2 (Day 1) + 1] for all subjects. Date of last dose will be taken from the last day the subject indicated the dose was taken in their daily subject diary or date of Study Drug Instillation recorded in the eCRF, whichever value is later.

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group using the Safety population. A categorical dosing compliance variable will also be derived as non-compliant (<80% or >125%) or compliant (≥80% and ≤125%) and summarized with discrete summary statistics. Under-compliance (<80%) and over-compliance (>125%) will also be separately summarized.

Subject listings of study drug accountability and diary entries 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:

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

Date of last dose will be taken from the last day the subject indicated the dose was taken in their daily subject diary.

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

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

Extent of treatment exposure (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 and dosing compliance will also be produced.

13. Efficacy Analyses

13.1 Primary Analyses

The primary efficacy endpoints of the study are:

- Inferior corneal staining (sign), Pre- to Post-CAE® at Day 57 (Week 8); and
- Ocular discomfort (symptom), Pre-CAE® at Day 57 (Week 8).

For both endpoints, change from baseline will be calculated as Visit – Baseline such that a positive difference indicates a worsening of dry eye signs or symptoms. In addition, treatment comparisons between active and placebo will be calculated as Active – Placebo, such that a negative result indicates a better

score for the active treatment (i.e., the active treatment had a smaller increase in dry eye signs or symptoms than the placebo group). Change scores from pre- to post-CAE® will be calculated as Post-CAE® Score – Pre-CAE® Score.

13.1.1 PRE-CAE® TO POST-CAE® CHANGE IN INFERIOR FLUORESCEIN STAINING

Pre-CAE® and Post-CAE® fluorescein staining in the inferior region of the cornea will be graded using the Ora Calibra® Corneal and Conjunctival Staining Scale. The Ora Calibra® Corneal and Conjunctival Staining Scale ranges from 0 to 4 ([redacted]), where grade 0 = None, [redacted] and 4 = Severe.

Pre-CAE® to Post-CAE® change in inferior corneal fluorescein staining scores will be summarized at Visit 6 (Day 57 ± 3) by treatment group for the study eye using quantitative summary statistics. Changes from baseline in Pre-CAE® to Post-CAE® change in inferior corneal fluorescein staining will be compared between 0.25% HL036 Ophthalmic Solution and placebo using an analysis of covariance (ANCOVA) model that adjusts for baseline Pre-CAE® to Post-CAE® change and site. In addition, the study site by treatment interaction will be explored in a separate analysis using observed data only to evaluate how the treatment effect may differ across study sites. In the case of a significant interaction at the 0.05 level, analyses will be performed by site to understand how the treatment effect differs across sites. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be conducted as sensitivity analyses to assess robustness of the results.

The primary analysis will use MCMC imputation to have a full accounting of the ITT population at Visit 6 (Day 57 ± 3). The MCMC method will be performed using the SAS procedure PROC MI. The SAS code for obtaining multiple imputation data is:

```
PROC MI DATA = INDATA SEED = 425754 OUT = OUTDATA NIMPUTE = 20
       MINIMUM = 0 MAXIMUM = 4 ROUND = 0.5;
    BY TREATMENT;
    MCMC INITIAL = EM;
    VAR BASE_PRE BASE_POST V6_PRE V6_POST;
RUN;
```

where

- *INDATA* is the name of the input dataset
- *OUTDATA* is the name of the output dataset
- *TREATMENT* is the name of the treatment group variable
- *BASE_PRE* is the baseline pre-CAE® inferior corneal fluorescein staining score in the study eye
- *BASE_POST* is the baseline post-CAE® inferior corneal fluorescein staining score in the study eye
- *V6_PRE* is the pre-CAE® inferior corneal fluorescein staining score in the study eye at Visit 6 (Day 57 ± 3)

- *V6_POST* is the post-CAE® inferior corneal fluorescein staining score in the study eye at Visit 6 (Day 57 ± 3)

If multiple imputation using MCMC fails to impute missing values using the above SAS code, imputation will be reattempted by adding the baseline pre-CAE® and post-CAE® total corneal fluorescein staining score in the study eye. If MCMC imputation is still not successful at imputing missing values, then multiple imputation will be reattempted by removal of the `MINIMUM`, `MAXIMUM`, and `ROUND` options.

After obtaining twenty complete data sets, calculating pre-CAE® to post-CAE® changes, and calculating changes from baseline, the following SAS code will be used to run the ANCOVA model on each data set and combine the results from the twenty analyses:

```
PROC MIXED DATA = OUTDATA;
    BY _IMPUTATION_;
    CLASS TREATMENT SITE;
    MODEL CFB = SITE BASELINE TREATMENT / SOLUTION COVB;
    LSMEANS TREATMENT / CL PDIFF;
    ODS OUTPUT LSMEANS = OUTLS DIFFS = OUTDIFFS;
RUN;
PROC SORT DATA=OUTLS; BY TREATMENT _IMPUTATION_; RUN;
PROC MIANALYZE DATA=OUTLS;
    BY TREATMENT;
    MODELEFFECTS ESTIMATE;
    STDERR STDERR;
RUN;

PROC SORT DATA=OUTDIFFS; BY _IMPUTATION_; RUN;
PROC MIANALYZE DATA=OUTDIFFS;
    MODELEFFECTS ESTIMATE;
    STDERR STDERR;
RUN;
```

where

- *TREATMENT* is the name of the treatment group variable
- *SITE* is the site id
- *BASELINE* is the baseline pre-CAE® to post-CAE® change in inferior corneal fluorescein staining score in the study eye
- *CFB* is the change from baseline in pre-CAE® to post-CAE® change in inferior corneal fluorescein staining score in the study eye at Visit 6 (Day 57 ± 3)
- *OUTLS* is the name of the output dataset that contains the statistical results for the treatment mean from the ANCOVA model that is run on each of the twenty imputation datasets
- *OUTDIFFS* is the name of the output dataset that contains the statistical results for the difference in treatment mean from the ANCOVA model that is run on each of the twenty imputation datasets

Similar SAS code will be used to conduct MCMC multiple imputation analysis for the t-test.

A sensitivity analysis will be performed on the ITT population using control-based pattern mixture model imputation. The SAS code for obtaining multiple pattern mixture model imputation data is:

```
PROC MI DATA = INDATA SEED = 988416 OUT = MDATA NIMPUTE = 1
      MINIMUM = 0 MAXIMUM = 4 ROUND = 0.5;
    MCMC IMPUTE=MONOTONE;
    VAR BASE_PRE BASE_POST V6_PRE V6_POST;
RUN;

PROC MI DATA = MDATA SEED = 253464 OUT = OUTDATA NIMPUTE = 20
      MINIMUM = . 0 0 0 0 MAXIMUM = . 4 4 4 4 ROUND = . 0.5 0.5 0.5 0.5;
    CLASS TREATMENT;
    MONOTONE REG(V6_PRE = BASE_PRE / DETAILS)
       REG(V6_POST = BASE_PRE BASE_POST V6_PRE / DETAILS);
    MNAR MODEL(V6_PRE V6_POST / MODELOBS=(TREATMENT='Placebo'));
    VAR TREATMENT BASELINE PRE_POST_CHG;
RUN;
```

where

- *INDATA* is the name of the input dataset
- *MDATA* is the name an intermediary dataset with a monotone missing pattern
- *OUTDATA* is the name of the output dataset
- *TREATMENT* is the name of the treatment group variable
- *BASE_PRE* is the baseline pre-CAE® inferior corneal fluorescein staining score in the study eye
- *BASE_POST* is the baseline post-CAE® inferior corneal fluorescein staining score in the study eye
- *V6_PRE* is the pre-CAE® inferior corneal fluorescein staining score in the study eye at Visit 6 (Day 57 ± 3)
- *V6_POST* is the post-CAE® inferior corneal fluorescein staining score in the study eye at Visit 6 (Day 57 ± 3)

Analysis of the resulting data will be as described for MCMC multiple imputation.

If multiple imputation using pattern mixture models fails to impute missing values using the above code, imputation will be reattempted utilizing baseline pre-CAE® and post-CAE® total corneal fluorescein staining score. In addition, imputation will be attempted by removing the `MINIMUM`, `MAXIMUM`, and `ROUND` options as described for MCMC multiple imputation.

Sensitivity analyses will also be performed on the ITT and PP populations using observed data only, and on the ITT population using LOCF methodology. An example of the SAS code implementation of the ANCOVA model for the observed data only and LOCF analyses is as follows:

```
PROC MIXED;
```

```
        CLASS SITE TREATMENT;
        MODEL CFB = SITE BASELINE TREATMENT / SOLUTION COVB;
        LSMEANS TREATMENT / CL PDIFF;
RUN;
```

Two sample t-tests and Wilcoxon rank sum tests will also be conducted for the observed data only (ITT and PP) and LOCF analyses.

Pre-CAE® to Post-CAE® change in inferior corneal fluorescein staining score change from baseline in the study eye at Visit 6 (Day 57 ± 3) will be displayed graphically in a bar chart with standard error bars by treatment group.

13.1.2 PRE-CAE® ORA CALIBRA® OCULAR DISCOMFORT SCALE

Ocular discomfort scores will be subjectively graded by the subjects using the Ora Calibra® Ocular Discomfort Scale at all scheduled visits. The ocular discomfort scale ranges from 0 to 4 where [redacted].

Changes from baseline in the pre-CAE® Ocular Discomfort Scale will be summarized at Visit 6 (Day 57 ± 3) by treatment group for the study eye using quantitative summary statistics. Changes from baseline will be compared between 0.25% HL036 Ophthalmic Solution and placebo using an ANCOVA model that adjusts for baseline and site. In addition, the study site by treatment interaction will be explored in a separate analysis using observed data only to evaluate how the treatment effect may differ across study sites. In the case of a significant interaction at the 0.05 level, analyses will be performed by site to understand how the treatment effect differs across sites. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Two sample t-tests and Wilcoxon rank sum test will also be conducted as sensitivity analyses to assess robustness of the results.

The primary analysis will use MCMC imputation on the ITT population at Visit 6 (Day 57 ± 3). SAS code for the multiple imputation analysis will resemble the code in Section 13.1.1. for inferior corneal fluorescein staining, except the random number seed for `PROC MI` will be `SEED = 469204` and the rounding parameter will be `round = 1`. Sensitivity analyses will be performed on the ITT and PP populations using observed data only, and on the ITT population using LOCF methodology and pattern mixture model imputation. The random number seeds for the monotone imputation and pattern mixture model imputation described in Section 13.1.1 will be `SEED = 597521` and `SEED = 1054602`, respectively.

Changes from baseline in the pre-CAE® Ocular Discomfort Scale in the study eye at Visit 6 (Day 57 ± 3) will be displayed graphically in a bar chart with standard error bars by treatment group.

13.2 Secondary Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, SD, median, min and max) and analyzed with two-sample t-tests comparing the treatment group to placebo. All visit-based data will be analyzed at each visit and change from baseline. Change scores from pre- to post-CAE® will be calculated as Post-CAE® Score – Pre-CAE® Score. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed where appropriate. Counts and frequencies will be used to summarize categorical variables by visit and treatment arm when applicable. No imputation will be performed for secondary efficacy variables. Listings for each secondary efficacy endpoint will be provided.

Corneal fluorescein staining by region and total, conjunctival lissamine green staining by region, conjunctival redness, unanesthetized Schirmer's test, TFBUT, OSDI©, VAS, ocular discomfort and dry eye symptoms, ocular discomfort during CAE®, pre- to post-CAE® changes, drop comfort assessment and changes from baseline in these measures will be analyzed by visit using paired t-tests, two-sample t-tests and Wilcoxon rank sum tests, as appropriate.

The worst symptom for each subject will be identified as the symptom with the highest average score during the run-in period (Days -14 to -1) as recorded in the subject diary. For morning, evening, and daily average assessments, the weekly averages of the worst symptom and each individual symptom will be analyzed using two-sample t-tests and Wilcoxon rank sum tests.

The following secondary efficacy endpoints will be tested:

- Fluorescein staining (Ora Calibra® scale) by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total staining
- Lissamine green staining (Ora Calibra® scale) by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total staining
- Conjunctival Redness
- Unanesthetized Schirmer's Test
- TFBUT
- OSDI©
- VAS
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Daily symptom diary (Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire)
- Ora Calibra® Drop Comfort assessment

13.2.1 FLUORESCEIN STAINING

Corneal and conjunctival fluorescein staining will be performed at all scheduled visits, on both eyes and graded using the Ora Calibra® Corneal and Conjunctival Staining Scale. Both pre- and post-CAE® assessments will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). The scale will grade the cornea and conjunctiva by five regions: inferior, superior, central, temporal, and nasal. The Ora Calibra® Corneal and Conjunctival Staining Scale ranges from 0 to 4 ([redacted]), where grade 0 = None, [redacted] and 4 = Severe.

Fluorescein staining scores will be summarized by visit, time point (pre- and post-CAE®), and region (5 regions, plus corneal sum, conjunctival sum, and total scores) for the study eye using quantitative summary statistics. The corneal sum score will be the sum of scores from the inferior, superior, and central regions. The conjunctival sum score will be the sum of scores from the nasal and temporal regions. The total score will be the sum of scores from all five regions.

Two-sample t-tests will be employed to compare treatment and placebo means at each visit and time point. The differences in means, two-sided 95% CIs for the difference in means and p-values will be reported. Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatments using ANCOVA models that adjust for baseline and site. The Least Squares (LS) means, LS mean differences, Standard Errors (SEs), two-sided 95% CIs for the difference in means and two-sided p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

Pre-CAE®, post-CAE® and pre-CAE® to Post-CAE® change in inferior corneal fluorescein staining score in the study eye will be displayed graphically in a line chart with standard error bars by visit and treatment group.

13.2.2 LISSAMINE GREEN STAINING

Corneal and conjunctival lissamine green staining will be performed at all visits, on both eyes and graded using the Ora Calibra® Corneal and Conjunctival Staining Scale. Both pre- and post-CAE® assessments will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). The scale will grade the cornea and conjunctiva by five regions: inferior, superior, central, temporal, and nasal. The Ora Calibra® Corneal and Conjunctival Staining Scale ranges from 0 to 4 ([redacted]), where grade 0 = None, [redacted] and 4 = Severe.

Lissamine green staining scores will be summarized by visit, time point, and region (5 regions, plus corneal sum, conjunctival sum, and total scores) for the study eye using quantitative summary statistics. The corneal sum score will be the sum of scores from the inferior, superior, and central regions. The conjunctival sum score will be the sum of scores from the nasal and temporal regions. The total score will be the sum of scores from all five regions.

Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means at each visit and time point. The differences in means, two-sided 95% CIs for the difference, in means and p-values will be reported. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two-sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

13.2.3 CONJUNCTIVAL REDNESS

The Ora Calibra® Conjunctival Redness Scale for Dry Eye will be performed on all scheduled visits. Both pre- and post-CAE® assessments will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). The conjunctival redness scale ranges from 0 to 4 ([redacted]) where [redacted]

Scores will be summarized for the study eye by visit, time point, and treatment group using quantitative summary statistics, including 95% CIs. Change from baseline will also be summarized. Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means at each visit. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

13.2.4 UNANESTHETIZED SCHIRMER'S TEST

Unanesthetized Schirmer's Test will be assessed on both eyes post-CAE® at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). 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.

Unanesthetized Schirmer's Test will be summarized for the study eye by visit using quantitative summary statistics. Change from baseline will be also summarized.

Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means at each visit. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatment arms using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

13.2.5 TEAR FILM BREAK-UP TIME

Tear film break-up time will be measured at all scheduled visits on both eyes. Both pre- and post-CAE® assessments will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). For each eye, two measurements will be recorded in seconds and averaged unless the two measurements are > 2 seconds apart and are each < 10 seconds, in which case, a third measurement will be taken and the two closest of the three will be averaged and used for analyses. If the differences between two sequential pairs of measurements are the same (e.g., 3, 6, 9 seconds), then the median of the three readings will be used for analysis.

Tear film break-up time will be summarized for the study eye by visit, time point, and treatment group using quantitative summary statistics. Change from baseline will also be summarized.

Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means at each visit and time point. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be

conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

13.2.6 Ocular Surface Disease Index©

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The OSDI© asks the following 12 questions at the subject level:

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

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

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

6) Reading?
7) Driving at night?
8) Working with a computer or bank machine (ATM)?
9) Watching TV?

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

10) Windy conditions?
11) Places or areas with low humidity (very dry)?
12) Areas that are air conditioned?

OSDI© will be assessed pre-CAE® at each visit at the subject level. The 5-unit scale for responses to the OSDI© is given by the following: [redacted]. The total OSDI© score is calculated by the following:

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

Note that the number of questions answered in the denominator should exclude those questions with a response of “N/A.” Continuous descriptive statistics, including two-sided 95% CIs, as well as changes from baseline will be summarized by treatment group and visit. Each individual response and the total OSDI© score will be presented separately.

Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means at each visit. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two-sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

13.2.7 Visual Analogue Scale

At every visit, subjects will be asked to rate each ocular symptom due to ocular dryness by placing a vertical mark on a horizontal line of length 100 mm to indicate the level of discomfort. 0 mm corresponds to "No Discomfort" and 100 mm corresponds to "Maximal Discomfort." Both pre- and post-CAE® assessments will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). Symptoms assessed are burning/stinging, itching, foreign body sensation, blurred vision, eye dryness, photophobia, and pain.

Symptom scores will be summarized by visit, time point, and treatment group using quantitative summary statistics, including two-sided 95% CIs. Change from baseline will also be summarized.

Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means at each visit and time point. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

13.2.8 Ora Calibra® Ocular Discomfort Scale

Ocular discomfort scores will be subjectively graded by the subjects using the Ora Calibra® Ocular Discomfort Scale at all scheduled visits. Both pre- and post-CAE® assessments will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). Ocular discomfort scores will also be assessed during the CAE® exposure, immediately upon entering the chamber and [redacted]. The ocular discomfort scale ranges from 0 to 4 where

[redacted]

13.2.8.1 Ora Calibra® Ocular Discomfort Scale Pre-, Post-, and Non-CAE®

Pre- and post-CAE® assessments of ocular discomfort will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). Ocular discomfort will also be assessed during the non-CAE® Visit 3 (Day 8 ± 1). Assessments and changes from baseline will be summarized by treatment group, visit and time point using continuous descriptive statistics, including two-sided 95% CIs. Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means at each visit and time point. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only for the study eye.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only for the study eye.

Pre-CAE®, post-CAE® and pre-CAE® to Post-CAE® change in ocular discomfort in the study eye will be displayed graphically in a line chart with standard error bars by visit and treatment group.

13.2.8.2 Ora Calibra® Ocular Discomfort Scale During CAE® Exposure

Ocular discomfort scores will be assessed [redacted] during the CAE® exposure. Assessments and changes from baseline will be summarized by treatment group, visit and time point using continuous descriptive statistics, including two-sided 95% CIs. The change from the 0 minutes assessment within the same visit and changes from baseline will also be summarized by treatment group, visit, and time point.

For both the ocular discomfort score and the change from 0 minutes, two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means at each visit and time point. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only for the study eye.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only for the study eye.

A mixed-effect model for repeated measures (MMRM) will also be used to compare treatment and placebo groups at Visits 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3) while accounting for the correlations among the repeated measurements during the CAE®. The model will include treatment group; time (nominal time will be used); treatment by time interaction, site, and baseline ocular discomfort score as fixed effects; and subject as the random effect. The following SAS code will be used:

```
PROC MIXED DATA = INDATA METHOD=ML;
       CLASS SUBJID TREATMENT TIME SITE;
       MODEL CHG_ODS = ODS_BASE SITE TREATMENT | TIME
              / SOLUTION COVB DDFM=KR;
       REPEATED TIME / TYPE = UN SUBJECT = SUBJID;
       LSMEANS TREATMENT TREATMENT*TIME/ CL PDIFF;
       ODS OUTPUT LSMEANS = OUTLS DIFFS = OUTDIFFS;
RUN;
```

where

- *SUBJID* is the subject ID
- *TREATMENT* is the name of the treatment group variable
- *TIME* is the nominal time of the measurement
- *SITE* is the site id
- *CHG_ODS* is the change from baseline ocular discomfort score
- *ODS_BASE* is the timepoint matched baseline ocular discomfort score in the study eye
- *OUTLS* is the name of the output dataset that contains the statistical results for the treatment means from the MMRM
- *OUTDIFFS* is the name of the output dataset that contains the statistical results for the differences in treatment means from the MMRM

If the MMRM does not converge with an unstructured covariance matrix, Toeplitz (`TYPE = TOEP`) and compound symmetry (`TYPE = CS`) structures will be utilized in order until convergence is achieved. If the MMRM with compound symmetry does not converge, MMRM statistical inferences will represented as not calculable.

LS means from the MMRM will be displayed graphically in a line graph with standard error bars by treatment group based on the MMRM analysis.

13.2.9 ORA CALIBRA® OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE

Ocular discomfort and dry eye symptoms will be assessed at all scheduled visits at the subject level in regard to how both eyes feel. Both pre- and post-CAE® assessments will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). Subjects will also grade the severity of their

dry eye syndrome symptoms each day during the at-home dosing period in their diary in the morning and in the evening before instilling the study drug. The Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire will be used, which includes rating of the severity of 5 symptoms: ocular discomfort, burning, dryness, grittiness, and stinging. Each symptom rating ranges from 0 to 5, where [redacted].

13.2.9.1 Assessments During Visits

Ocular discomfort and dry eye symptoms will be summarized by visit, time point, and treatment group using quantitative summary statistics including two-sided 95% CIs. Change from baseline will be also summarized. Two-sample t-tests will be employed to compare treatment and placebo means as well as the changes from baseline at each visit and time point. Comparisons between treatment groups and between all active groups and placebo will also be conducted. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two-sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

13.2.9.2 Diary Assessments

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 and evening, before instilling the study drug. The average of the morning and evening assessments will be calculated for each week and symptom.

The worst symptom for each subject will be identified as the symptom with the highest average score during the run-in period (Days -14 to -1) as recorded in the subject diary. First daily averages, per symptom, from morning and evening diary entries will be calculated. In the case of ties, the worst symptom will be selected in the order of ocular discomfort, burning, dryness, grittiness and stinging from among those with the highest average. Then the daily averages will be averaged for each symptom. The highest average symptom is called the worst symptom for each subject.

The worst symptom and each individual symptom will be summarized by week, time point (morning, evening, and daily average), and treatment group using quantitative summary statistics including two-sided 95% CIs. The average post-treatment score for the worst symptom and each individual symptom will also be summarized by time point and treatment group. Change from baseline will be also summarized. Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means as well as the changes from baseline at each day and time point. The differences in means, two-sided 95%

CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only.

Changes from baseline will be compared between treatment groups using ANCOVA models that adjust for baseline and site. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in means, and two-sided p-values will be reported. Two-sample t-tests and Wilcoxon rank sum tests will also be conducted. Within each treatment arm, paired t-tests will be conducted to compare change from baseline. Analyses will be performed on the ITT population with observed data only.

An MMRM will also be used to compare treatment and placebo groups while accounting for the correlations among the repeated weekly scores. Separate models will be estimated for the daily average scores, the average morning scores, and the average evening scores. The model will include treatment group, study week, site, treatment by week interaction, and baseline symptom score as fixed effects, and subject as the random effect. Baseline symptom score will be the average score of the run-in period. The following SAS code will be used:

```
PROC MIXED DATA = INDATA METHOD=ML;
       CLASS SUBJID TREATMENT WEEK SITE;
       MODEL CHG = ODS_BASE SITE TREATMENT | WEEK
              / SOLUTION COVB DDFM=KR;
       REPEATED WEEK / TYPE = UN SUBJECT = SUBJID;
       LSMEANS TREATMENT TREATMENT*WEEK/ CL PDIFF;
       ODS OUTPUT LSMEANS = OUTLS DIFFS = OUTDIFFS;
RUN;
```

where

- *SUBJID* is the subject ID
- *TREATMENT* is the name of the treatment group variable
- *SITE* is the site id
- *WEEK* is the study week
- *CHG* is the change from baseline symptom score
- *ODS_BASE* is the baseline symptom score
- *OUTLS* is the name of the output dataset that contains the statistical results for the treatment means from the MMRM
- *OUTDIFFS* is the name of the output dataset that contains the statistical results for the differences in treatment means from the MMRM

If the MMRM does not converge with an unstructured covariance matrix, Toeplitz (`TYPE = TOEP`) and compound symmetry (`TYPE = CS`) structures will be utilized in order until convergence is achieved. If the

MMRM with compound symmetry does not converge, MMRM statistical inferences will represented as not calculable.

LS means of the change from baseline from the MMRM will be displayed graphically in a bar chart with standard error bars by treatment group and week based on the MMRM analysis. Separate figures will be generated for daily average, morning and evening scores.

Weekly average scores of ocular discomfort, each individual symptom and worst symptom will be displayed graphically by week in a line plot by treatment group. Separate figures will be generated for daily average, morning and evening scores.

Additional analyses of diary assessments will involve stratification of subjects by time to CAE® qualification at Visit 2 (Day 1) with ITT population with observed data only. Figures will be produced as described in this section for the stratified analyses.

The time to CAE® qualification is the first time point in the CAE® when the ocular discomfort score ≥ 3 for two consecutive time points in the study eye if a subject has an ocular discomfort score < 3 at time 0, and the first time point in the CAE® when the ocular discomfort score = 4 for two consecutive time points in the study eye if a subject has an ocular discomfort score = 3 at time 0. An ocular discomfort score of 4 is not allowed at time 0.

13.2.10 ORA CALIBRA® DROP COMFORT ASSESSMENT

Drop comfort will be assessed for each eye immediately, and at 1 and 2 minutes following initial dosing at Visit 2 (Day 1) using the Ora Calibra® Drop Comfort Scale. The scale ranges from 0 to 10, with 0 = Very Comfortable and 10 = Very Uncomfortable. Drop comfort will be summarized by visit and timepoint using quantitative summary statistics. Two-sample t-tests and Wilcoxon rank sum tests will be employed to compare treatment and placebo means. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Analyses will be performed on the ITT population with observed data only for the study eye.

Descriptions of drop comfort will be assessed at [redacted] following initial dosing at Visit 2 (Day 1) using the Ora Calibra® Drop Comfort Questionnaire. On this questionnaire, subjects will be asked to choose three words that best describe how each eye drop feels in both of his/her eyes. The positive responses are comfortable, cool, refreshing, smooth, and soothing. The negative responses include burning, filmy, stinging, sticky, thick, gritty, and irritating. Subjects may also select “other” and write in a response of their choosing, which may be either a positive or a negative response. Drop Comfort Questionnaire responses will be summarized by treatment group using qualitative summary statistics. Subjects with at least one negative response as well as subjects with at least one positive response will also be summarized by treatment group. Analyses will be performed on the ITT population with observed data only.

14. Safety Analyses

All safety analyses will be conducted using the Safety Population.

14.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. All AEs will be coded using MedDRA Version 20.1.

Treatment-emergent adverse events (TEAE) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated

An overall summary will be presented that includes the number of AEs, TEAEs, SAEs, treatment-emergent serious adverse events (TE-SAE), number of subjects with TEAEs by maximum severity, and number of subjects with TEAEs by relationship to study drug. The summary will also include the number and percentage of subjects withdrawn due to an AE, the number and percentage of subjects with an AE resulting in death, and the number and percentage of subjects who experienced at least one AE, TEAE, SAE and TE-SAE, by treatment group and for all subjects. This summary will include breakdowns of AEs further categorized as ocular or non-ocular as well as the number and percentage of resolved ocular AEs and the mean number of days until AE resolution for resolved ocular AEs.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by SOC and PT. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject and event level as well as for study and fellow eyes separately. 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 summary, SOC will be listed in order of descending frequency for all subjects; PTs will be listed in order of descending frequency for all subjects within each SOC.

Separate summaries will be provided for the following categories of AEs:

- Ocular AEs
- Non-ocular AEs
- Ocular TEAEs
- Non-ocular TEAEs

- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs
- Serious AEs

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

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

Summaries of TEAEs by maximal severity will be presented for ocular AEs and non-ocular AEs 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 PT within the same SOC, the subject will be counted once under the maximal severity.

The relationship of each adverse event to the investigational product (IP) should be determined by the investigator (in a blinded manner) using these explanations:

- *Definite:* Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
- *Probable:* Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
- *Possible:* Relationship exists when the AE follows a reasonable sequence from the time of administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

All possible, probable, and definite TEAEs are considered as treatment-related TEAEs.

The occurrence of non-ocular and ocular TEAEs will also be tabulated by SOC, PT, and study day of onset (prior to Day 9, Day 9 to Day 29, After Day 29).

All AEs will be presented in a subject listing that classifies each AE as ocular or non-ocular and indicates whether it is a TEAE. Separate listings will be produced for SAEs, AEs leading to treatment discontinuation, and AEs leading to death.

14.2 Visual Acuity (ETDRS)

The visual acuity (VA) procedure will be performed at each visit pre-CAE®. The logMAR VA must be assessed using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual Acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit-lamp examination). Subjects should use their most recent correction to attain their best-corrected visual acuity (BCVA).

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. A subject listing of visual acuity will also be produced.

14.3 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, and lid will be performed at each visit, and potentially at an Early Termination Visit. Both pre- and post-CAE® examinations will be made at Visits 1 (Day -14 ± 1), 2 (Day 1), 4 (Day 15 ± 2), 5 (Day 29 ± 2), and 6 (Day 57 ± 3). The results will be graded as Normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS). Abnormal findings will be described.

The results will be summarized using counts and percentages for each treatment group at each visit and time point 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 Dilated Fundoscopy Examination

A dilated fundoscopy exam will be performed during the study post-CAE® at Visits 1 (Day -14 ± 1) and 6 (Day 57 ± 3), and potentially at unscheduled visit assessments. Observations of the vitreous, retina, macula, choroid, and optic nerve will be graded as Normal, Abnormal NCS, or Abnormal CS. Abnormal findings will be described.

The results will be summarized using counts and percentages for each treatment group 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 dilated fundoscopy parameters will also be provided comparing Visit 6 (Day 57 ± 3) to baseline (Visit 1). A subject listing of the dilated fundoscopy parameters will also be produced.

14.5 Intraocular Pressure (IOP)

IOP will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg post-CAE® at Visits 1 (Day -14 ± 1) and 6 (Day 57 ± 3), and potentially at unscheduled visit assessments. A single measurement is made to obtain a determination of IOP. The same tonometer employing the investigator's standard technique will be used throughout the study. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject.

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.

14.6 Immunogenicity to HL036 in Serum

Analyses of immunogenicity data will be conducted as ad-hoc analyses. The anticipated ad-hoc analyses of immunogenicity are as follows.

Immunogenicity will be summarized using discrete summary statistics. Counts and proportions of subjects with anti-drug antibodies (ADA) will be presented by visit and treatment group. Exact 95% Clopper-Pearson CIs will be presented. Treatment groups will be compared using Fisher's exact test, and exact 95% confidence intervals for the pairwise proportion differences will be constructed.

Antibody titer of subjects positive for ADA will be summarized using continuous descriptive statistics and presented by visit and treatment group. Treatment groups will be compared using two-sample t-tests. The differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Wilcoxon rank sum tests will also be conducted.

15. Interim Analyses

No interim analyses are planned for this study.

16. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

17. Revision History

The following revisions were made to SAP Version 2.0.

SAP Section	Revision	Rationale
3.1, 13.2.8	Changed [redacted]	CAE exposure is for [redacted]
13.1.1	Added semicolon in SAS code	Correct typographic error
13.1.1, 13.1.2	Specified that the study site by treatment interaction would be tested using observed data only	Common techniques are not available for testing this interaction using MCMC
13.2.9.2	Added detail on diary figures	Improve clarity on diary figures
19	Removed duplicate Urine Pregnancy Test listing	Remove redundant listing
20	Revised diary figure titles and split LS Means figure and average symptom score figures into two figures	Improve clarity on diary figures

18. Tables

Tables that will be included in the topline delivery are shown in boldface font. Tables in italicized font may be generated under specified conditions.

Table Number	Title	Population
TABLE 14.1.1	**SUBJECT DISPOSITION**	**ALL RANDOMIZED SUBJECTS**
TABLE 14.1.2.1	**DEMOGRAPHICS**	**ITT**
TABLE 14.1.2.2	DEMOGRAPHICS	SAFETY
TABLE 14.1.3.1	**BASELINE DISEASE CHARACTERISTICS (STUDY EYE)**	**ITT**

Table Number	Title	Population
TABLE 14.1.3.2	OCULAR MEDICAL HISTORY	ITT
TABLE 14.1.3.3	NON-OCULAR MEDICAL HISTORY	ITT
TABLE 14.1.4.1	CONCOMITANT OCULAR MEDICATIONS BY TREATMENT GROUP, DRUG CLASS AND PREFERRED NAME	ITT
TABLE 14.1.4.2	CONCOMITANT NON-OCULAR MEDICATIONS BY TREATMENT GROUP, DRUG CLASS AND PREFERRED NAME	ITT
TABLE 14.1.5	SUBJECT POOLING BY SITE	ALL RANDOMIZED SUBJECTS
TABLE 14.2.1.1.1	**PRE- TO POST-CAE CHANGE IN INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA SCALE)**	**ITT WITH MCMC**
TABLE 14.2.1.1.1.1	*PRE- TO POST-CAE CHANGE IN INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA SCALE) SITE ANALYSIS*	*ITT WITH MCMC*
TABLE 14.2.1.1.2	PRE- TO POST-CAE CHANGE IN INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA SCALE)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.1.1.3	PRE- TO POST-CAE CHANGE IN INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA SCALE)	ITT WITH LOCF
TABLE 14.2.1.1.4	PRE- TO POST-CAE CHANGE IN INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA SCALE)	ITT WITH PMM
TABLE 14.2.1.1.5	PRE- TO POST-CAE CHANGE IN INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA SCALE)	PP WITH OBSERVED DATA ONLY
TABLE 14.2.1.2.1	**PRE-CAE OCULAR DISCOMFORT (ORA CALIBRA SCALE)**	**ITT WITH MCMC**
TABLE 14.2.1.2.1.1	*PRE-CAE OCULAR DISCOMFORT (ORA CALIBRA SCALE) SITE ANALYSIS*	*ITT WITH MCMC*

Table Number	Title	Population
TABLE 14.2.1.2.2	PRE-CAE OCULAR DISCOMFORT (ORA CALIBRA SCALE)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.1.2.3	PRE-CAE OCULAR DISCOMFORT (ORA CALIBRA SCALE)	ITT WITH LOCF
TABLE 14.2.1.2.4	PRE-CAE OCULAR DISCOMFORT (ORA CALIBRA SCALE)	ITT WITH PMM
TABLE 14.2.1.2.5	PRE-CAE OCULAR DISCOMFORT (ORA CALIBRA SCALE)	PP WITH OBSERVED DATA ONLY
TABLE 14.2.2.1	**FLUORESCEIN CORNEAL AND CONJUNCTIVAL STAINING (ORA CALIBRA SCALE)**	**ITT WITH OBSERVED DATA ONLY**
TABLE 14.2.2.2	LISSAMINE GREEN CORNEAL AND CONJUNCTIVAL STAINING (ORA CALIBRA SCALE)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.3	ORA CALIBRA CONJUNCTIVAL REDNESS SCALE FOR DRY EYE	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.4	UNANESTHETIZED SCHIRMER'S TEST (MM)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.5	TEAR FILM BREAK-UP TIME (SECONDS)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.6	OCULAR SURFACE DISEASE INDEX (OSDI)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.7	**VISUAL ANALOGUE SCALE**	**ITT WITH OBSERVED DATA ONLY**

Table Number	Title	Population
TABLE 14.2.2.8	**ORA CALIBRA OCULAR DISCOMFORT SCALE**	**ITT WITH OBSERVED DATA ONLY**
TABLE 14.2.2.9	ORA CALIBRA OCULAR DISCOMFORT SCALE (DURING CAE)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.10	ORA CALIBRA OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.11.1	ORA CALIBRA OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE (DIARY)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.11.2	**ORA CALIBRA OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE (DIARY) STRATIFIED BY TIME TO QUALIFYING DURING CAE**	**ITT WITH OBSERVED DATA ONLY**
TABLE 14.2.2.12	ORA CALIBRA DROP COMFORT SCALE	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.2.13	ORA CALIBRA DROP COMFORT QUESTIONNAIRE	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3	SUMMARY OF ANALYSES	ITT WITH MCMC / ITT WITH OBSERVED DATA ONLY
TABLE 14.3.1.1	**ADVERSE EVENT SUMMARY**	**SAFETY**
TABLE 14.3.1.2	ALL OCULAR ADVERSE EVENTS	SAFETY
TABLE 14.3.1.3	ALL NON-OCULAR ADVERSE EVENTS	SAFETY
TABLE 14.3.1.4	**ALL OCULAR TREATMENT-EMERGENT ADVERSE EVENTS**	**SAFETY**

Table Number	Title	Population
TABLE 14.3.1.5	ALL NON-OCULAR TREATMENT-EMERGENT ADVERSE EVENTS	SAFETY
TABLE 14.3.1.6	ALL OCULAR TREATMENT-RELATED TREATMENT-EMERGENT ADVERSE EVENTS	SAFETY
TABLE 14.3.1.7	ALL NON-OCULAR TREATMENT-RELATED TREATMENT-EMERGENT ADVERSE EVENTS	SAFETY
TABLE 14.3.1.8	**ALL SERIOUS ADVERSE EVENTS**	**SAFETY**
TABLE 14.3.1.9	ALL OCULAR TREATMENT-EMERGENT ADVERSE EVENTS BY MAXIMAL SEVERITY	SAFETY
TABLE 14.3.1.10	ALL NON-OCULAR TREATMENT-EMERGENT ADVERSE EVENTS BY MAXIMAL SEVERITY	SAFETY
TABLE 14.3.1.11	ALL OCULAR TREATMENT-EMERGENT ADVERSE EVENTS BY STUDY DAY OF ONSET	SAFETY
TABLE 14.3.1.12	ALL NON-OCULAR TREATMENT-EMERGENT ADVERSE EVENTS BY STUDY DAY OF ONSET	SAFETY
TABLE 14.3.2	VISUAL ACUITY - LOGMAR	SAFETY
TABLE 14.3.3.1	SLIT LAMP BIOMICROSCOPY	SAFETY
TABLE 14.3.3.2	SHIFT IN SLIT LAMP BIOMICROSCOPY	SAFETY
TABLE 14.3.4.1	DILATED FUNDOSCOPY	SAFETY
TABLE 14.3.4.2	SHIFT IN DILATED FUNDOSCOPY	SAFETY
TABLE 14.3.5	INTRAOCULAR PRESSURE	SAFETY
TABLE 14.3.6	COMPLIANCE WITH STUDY DRUG	SAFETY
TABLE 14.3.7	EXPOSURE TO STUDY DRUG	SAFETY

19. Listings

Listing Number	Title
LISTING 16.1.7	RANDOMIZATION SCHEDULE
LISTING 16.2.1	SUBJECT DISPOSITION
LISTING 16.2.2	PROTOCOL DEVIATIONS
LISTING 16.2.3	STUDY POPULATION INCLUSION
LISTING 16.2.4.1	DEMOGRAPHICS
LISTING 16.2.4.2	OCULAR MEDICAL HISTORY
LISTING 16.2.4.3	NON-OCULAR MEDICAL HISTORY
LISTING 16.2.4.4	PRIOR AND CONCOMITANT OCULAR MEDICATIONS
LISTING 16.2.4.5	PRIOR AND CONCOMITANT NON-OCULAR MEDICATIONS
LISTING 16.2.5.1	IN-OFFICE RUN--IN INSTILLATION
LISTING 16.2.5.2	RUN-IN KIT ASSIGNMENT
LISTING 16.2.5.3	IN-OFFICE STUDY DRUG INSTILLATION
LISTING 16.2.5.4	STUDY DRUG EXPOSURE AND DOSING COMPLIANCE
LISTING 16.2.5.5	STUDY DRUG ACCOUNTABILITY
LISTING 16.2.6.1	FLUORESCEIN CORNEAL AND CONJUNCTIVAL STAINING (ORA CALIBRA SCALE)
LISTING 16.2.6.2	LISSAMINE GREEN CORNEAL AND CONJUNCTIVAL STAINING (ORA CALIBRA SCALE)
LISTING 16.2.6.3	CONJUNCTIVAL REDNESS
LISTING 16.2.6.4	UNANESTHETIZED SCHIRMER'S TEST
LISTING 16.2.6.5	TEAR FILM BREAK UP TIME (TFBUT)
LISTING 16.2.6.6	OCULAR SURFACE DISEASE INDEX (OSDI)
LISTING 16.2.6.7	VISUAL ANALOGUE SCALE
LISTING 16.2.6.8	ORA CALIBRA OCULAR DISCOMFORT SCALE
LISTING 16.2.6.9	ORA CALIBRA OCULAR DISCOMFORT SCALE (DURING CAE)

Listing Number	Title
LISTING 16.2.6.10	ORA CALIBRA OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE
LISTING 16.2.6.11	OCULAR DISCOMFORT AND DRY EYE SYMPTOMS REPORTED IN THE SUBJECT DIARY
LISTING 16.2.6.12	ORA CALIBRA DROP COMFORT SCALE
LISTING 16.2.6.13	ORA CALIBRA DROP COMFORT QUESTIONNAIRE
LISTING 16.2.7.1	ALL ADVERSE EVENTS
LISTING 16.2.7.2	SERIOUS ADVERSE EVENTS
LISTING 16.2.7.3	ADVERSE EVENTS LEADING TO TREATMENT DISCONTINUATION
LISTING 16.2.7.4	ADVERSE EVENTS LEADING TO DEATH
LISTING 16.2.8.1	VISUAL ACUITY - LOGMAR
LISTING 16.2.8.2	SLIT LAMP BIOMICROSCOPY
LISTING 16.2.8.3	DILATED FUNDOSCOPY
LISTING 16.2.8.4	INTRAOCULAR PRESSURE (IOP)
LISTING 16.2.8.5	BLOOD DRAW FOR IMMUNOGENICITY
LISTING 16.2.8.6	URINE PREGNANCY TEST

20. **Figures**

Figure Number	Title	Population
FIGURE 14.2.1.1	**PRE- TO POST-CAE CHANGE IN INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA SCALE) CHANGE FROM BASELINE**	**ITT WITH MCMC**
FIGURE 14.2.1.2	**PRE-CAE OCULAR DISCOMFORT (ORA CALIBRA SCALE) CHANGE FROM BASELINE**	**ITT WITH MCMC**
FIGURE 14.2.2.1	INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA SCALE) BY VISIT	ITT WITH OBSERVED DATA ONLY

Figure Number	Title	Population
FIGURE 14.2.2.2	ORA CALIBRA OCULAR DISCOMFORT (OUTSIDE CAE) BY VISIT	ITT WITH OBSERVED DATA ONLY
FIGURE 14.2.2.3	ORA CALIBRA OCULAR DISCOMFORT SCALE (DURING CAE) CHANGE FROM BASELINE	ITT WITH OBSERVED DATA ONLY
FIGURE 14.2.2.4.1	ORA CALIBRA ORA CALIBRA OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE (DIARY) CHANGE FROM BASELINE	ITT WITH OBSERVED DATA ONLY
FIGURE 14.2.2.4.2	WEEKLY AVERAGE ORA CALIBRA OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE (DIARY)	ITT WITH OBSERVED DATA ONLY
FIGURE 14.2.2.5.1	**ORA CALIBRA ORA CALIBRA OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE (DIARY) CHANGE FROM BASELINE BY CAE QUALIFICATION**	**ITT WITH OBSERVED DATA ONLY**
FIGURE 14.2.2.5.2	**WEEKLY AVERAGE ORA CALIBRA OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE (DIARY) BY CAE QUALIFICATION**	**ITT WITH OBSERVED DATA ONLY**