STATISTICAL ANALYSIS PLAN

A Phase 2, Multicenter, Randomized, Double-Masked and Placebo-Controlled Study Evaluating the Efficacy of Two Concentrations (0.10%, 0.25%) of HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye

Sponsor: HanAll Biopharma, Co., Ltd.

Protocol Number: HL036-DED-US-P201

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Date: 15-Mar-2018

Version: 1.0

A Single-Center, Phase 2a, Randomized, Double-Masked, Clinical Study to Assess the Safety, Tolerability, and Pharmacodynamic Activity of ADX-102 Ophthalmic Solution in Subjects with Dry Eye Syndrome

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Date: **15-Mar-2018**

Statistical Analysis Plan Approval

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List of Abbreviations

ADA	Anti-drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best Corrected Visual Acuity
CAE	Controlled Adverse Environment
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
DMP	Data Management Plan
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
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
NCS	Not clinically significant
OSDI	Ocular Surface Disease Index
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAAS	Software-as-a-Service
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Serious Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
VA	Visual Acuity

VAS	Visual Analogue Scale
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol HL036-DED-US-P201 Amendment 1, dated 31OCT2017.

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 objective of this study is to compare the safety and efficacy of 0.10% and 0.25% HL036 Ophthalmic Solutions to placebo for the treatment of the signs and symptoms of dry eye.

3. Study Variables

3.1 Primary Efficacy Endpoints

The primary efficacy endpoints are:

- Change from baseline in pre-Controlled Adverse Environment® (CAE®) inferior corneal staining score in the designated study eye as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining at Visit 6 (Day 57, Week 8)

and

- Change from baseline in pre-CAE® ocular discomfort in the designated study eye as assessed by the Ora Calibra® Ocular Discomfort Scale at Visit 6 (Day 57, Week 8)

3.2 Secondary Efficacy Endpoints

- Fluorescein staining by region: central, superior, inferior, temporal, nasal and corneal sum as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining at all time points

- Lissamine green staining by region: central, superior, inferior, temporal, nasal, and conjunctival sum as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Lissamine Staining at all time points
- TFBUT© at all timepoints assessed
- Conjunctival redness as assessed by the Ora Calibra® Conjunctival Redness Scale for Dry Eye at all timepoints assessed
- Schirmer's Test (unanesthetized) at all timepoints assessed
- Symptoms as assessed by the Ora Calibra® Ocular Discomfort Scale and Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire at all timepoints
- Visual Analog Scale (VAS) Ocular Discomfort at all timepoints assessed
- OSDI© at all timepoints assessed
- Drop comfort as assessed by the Ora Calibra® Drop Comfort Scale, and the Ora Calibra® Drop Comfort Questionnaire at all timepoints assessed
- Daily diary
- Tear mediators

  Change from baseline and change from pre- to post-CAE® will also be assessed where appropriate.

3.3 Safety Variables

The safety variables include the following:

- Incidence and severity of ocular Adverse Events (AE)
- Incidence and severity of non-ocular AEs
- Best-Corrected Visual Acuity (BCVA) at all visits
- Slit-lamp biomicroscopy at all visits
- Drop comfort assessment (Visit 2)
- Intraocular pressure (IOP) (Visits 1 and 6)
- Dilated fundoscopy (Visits 1 and 6)
- Immunogenicity to HL036 in Serum (Visits 2, 4, 5, and 6)

3.4 Statistical Hypotheses

The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided.

H_{01}: There is no difference between HL036 ophthalmic solution (0.25% or 0.10%) and placebo in the change from baseline of the pre-CAE® 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® inferior corneal fluorescein staining at Visit 6 (Day 57 ± 3) using the Ora Calibra® scale is less with HL036 ophthalmic solution (0.25% or 0.10%) than with placebo.

H_{02}: There is no difference between HL036 ophthalmic solution (0.25% or 0.10%) 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 HL036 ophthalmic solution (0.25% or 0.10%) than with placebo.

4. Study Design and Procedures

4.1 General Study Design

This is a Phase 2, 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 and will be instructed to follow a BID-dosing regimen:

- HL036 0.25% Ophthalmic Solution
- HL036 0.10% Ophthalmic Solution
- Placebo, HL036 Ophthalmic Solution

Subjects, Sponsor, CRO 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 twice daily and will complete daily 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.

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 table 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:

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

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.

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							
Study Drug Dispensation				X	X[2]		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[1]									X[1]	
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
Tear Collection			X							X	
Blood Sampling for Immunogenicity Testing				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	
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
Exit Subject from Study											X

[1] To women of child-bearing potential, as defined. [2] The Visit 2 study drug kit is redispensed at Visit 3.

5. Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

Prior to initiation of study run-in (at Visit 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 and exclusion criteria are met at Visits 1 and 2, each qualifying subject will then be assigned a randomization number at the end of Visit 2.

A randomization schedule will be generated using block randomization. Blocks of randomization numbers will be distributed to sites, such that there will be an approximate equal number of subjects assigned to each of the three treatment arms at each site. The site staff will dispense to the patient the study kit labeled with the corresponding randomization number. The randomization number will be recorded on the patient's source document and eCRF. A new kit will be dispensed at Visits 2, 4, and 5 based on the subject's randomization. The Visit 2 kit will be re-dispensed at Visit 3. The Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the study.

5.2 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.

6. Sample Size and Power Considerations

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

This study is expected to enroll 50 subjects in each of the three treatment arms, for a total of 150 randomized subjects. Assuming a 10% drop out rate, 45 subjects per group are expected to complete the study.

Assuming a common standard deviation in the change from baseline for the pre-CAE® inferior corneal fluorescein staining of 0.72 units, a sample size of 45 subjects per group will have 90% power to detect a difference of 0.5 units between each of the active treatment groups and the placebo group using a two-sample t-test at a significance level of 0.05. A sample size of 45 subjects per treatment arm will have 90% power to detect a mean difference of 0.80 units in the change from baseline for the pre-CAE® ocular discomfort as assessed by the Ora Calibra® Ocular Discomfort Scale, assuming a standard deviation of 1.15 units. Using an analysis of covariance model (ANCOVA) for each primary

endpoint should yield standard deviations no greater than those from a two-sample t-test. Therefore, the power for each endpoint for both the sign and the symptom is 81%, assuming independence between the endpoints. The power for both the sign and the symptom in both active treatments is 66%, assuming independence of treatments.

7. Data Preparation

Electronic Case Report Forms (eCRF) will be developed by Statistics and Data Corporation, Incorporated (SDC). Data from source documents will be entered into the eCRF by site personnel. All users will complete role-based system and study-specific eCRF training prior to receiving access to the study database. User access will be granted based on a user's role in the study and will be controlled through individual login credentials including a unique User ID and password.

The clinical study database will be developed and tested in iMedNet™. iMedNet™ is delivered as a single-instance multi-tenant Software-as-a-Service (SaaS) EDC system and is developed, maintained, and hosted by MedNet Solutions located in Minnetonka, Minnesota. Therefore, over the duration of the study, MedNet Solutions may apply system updates to the EDC system as part of their continuous improvement efforts.

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.

8. Analysis Populations

Analysis populations include the intent-to-treat (ITT) population, the per-protocol (PP) population, and the Safety population. The statistical analysis of safety data will be performed for the Safety population. The analysis of baseline and efficacy data will be performed for the ITT population. The primary efficacy analysis will also be performed on the PP population as sensitivity analyses.

8.1 Intent-to-Treat

The ITT population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.

8.2 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. Subjects in the PP population will be analyzed as treated.

8.3 Safety

The Safety population includes all randomized subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated. In the event that one or more subjects are exposed to multiple treatments, analyses will be conducted using all combinations of treatment assignments for these subjects.

9. General Statistical Considerations

9.1 Unit of Analysis

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

Study Eye/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 worst eye will be the eye with worse (higher) inferior corneal staining pre-CAE® at Visit 2. If the inferior corneal staining is the same in both eyes, then the worst eye will be the eye with the highest ocular discomfort pre-CAE® at Visit 2. If the ocular discomfort 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 primary efficacy analyses will be performed using Markov Chain Monte Carlo (MCMC) multiple imputation methodology for missing values. An analysis using observed data only will also be performed for the primary efficacy variables. As additional sensitivity analyses, Last Observation Carried Forward (LOCF) methodology and imputation via pattern mixture models will also be used to impute missing data for the analyses of the primary efficacy variables.

For the LOCF analyses of the primary efficacy variables at Day 57 (Visit 6), 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.

No secondary efficacy endpoints or safety endpoints will be imputed.

9.3 Definition of Baseline

Baseline measures are defined as the last non-missing measure prior to the initiation of study treatment, usually at Visit 2. If a measure is taken both pre-CAE® and post-CAE®, the baseline will be the time point matched value. For the non-CAE® Visit 3, the baseline will be the pre-CAE® value. For changes from pre-CAE® to post-CAE®, the baseline will be the last non-missing change from pre-CAE® to post-CAE® prior to initiation of study treatment. For measures from daily subject diaries, baseline is defined as the average of all days during the run-in period. Change from baseline will be calculated as follow-up visit minus baseline value.

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 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. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition. For the purpose of summarization, medical history, concurrent therapies, and adverse events will be coded to Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug dictionaries, as appropriate.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include 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".

9.5 Adjustments for Multiplicity

This is a phase 2 trial that is primarily exploratory in nature. As such, to claim success for the study significance is required for both the primary sign and the primary symptom, and for both active treatments. Hence, no multiplicity adjustment is necessary.

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 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, 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. 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 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 and description of each deviation.

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

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

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

Age (years) will be summarized 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 for age category, sex, race, ethnicity and iris color. Iris color will be summarized for the right eye (OD) and left eye (OS) separately.

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

11.2 Pretreatment Variables

Baseline disease characteristics will be summarized by treatment group using continuous descriptive statistics for pre-CAE® Ora Calibra® Ocular Discomfort Scale, pre-CAE® inferior fluorescein staining, pre-CAE® inferior lissamine green staining, total OSDI© score, BCVA, pre-CAE® TFBUT, unanesthetized Schirmer's test, and IOP. The scale for each assessment is provided in the respective subsection in Section 14 of this SAP.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using MedDRA Version 20.1.

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. Non-ocular medical history will be similarly summarized at the subject and event 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.

12.2 Prior and Concomitant Medications

Concomitant medications will be coded using WHO Drug Global B3 Dictionary September 2017 and summarized 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.

Concomitant medications will be summarized using the ITT population. Prior medications will be provided in subject listings, but will not be summarized. Ocular and non-ocular medications will be summarized separately. Medications will be tabulated for each treatment group 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 medications will be generated separately for ocular and non-ocular data.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

Subjects will be instructed on proper instillation and storage of study drug at the end of Visits 1, 2, 3, 4 and 5, and given written instructions. The used and unused study drug vials will be collected at each visit from Visit 2 up to and including Visit 6 to assess dosing compliance. Dosing compliance will be based off of the used and unused vial count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of used 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 doses expected as follows:

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

The number of doses taken will be calculated from the number of used vials on the drug accountability case report form (CRF). If a randomized subject discontinues from the study on Day 1, the number of

doses expected will be 1. Otherwise, the number of doses expected will be calculated as 2 x [(date of completion/discontinuation – date of Visit 2 (Day 1))] for all subjects.

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.

A subject listing of dosing compliance will also be produced.

13.2 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

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 will also be produced.

14. Efficacy Analyses

14.1 Primary Analysis

The two coprimary endpoints are:

- Change from baseline in the pre-CAE® inferior corneal fluorescein staining at Visit 6 (Day 57 ± 3), as measured on the Ora Calibra® scale
- Change from baseline in the pre-CAE® ocular discomfort score at Visit 6 (Day 57 ± 3), as measured on the Ora Calibra® Ocular Discomfort Scale

For both coprimary 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).

14.1.1 PRE-CAE® INFERIOR FLUORESCEIN STAINING

Pre-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.

Changes from baseline in the pre-CAE® inferior 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 will be compared between each dose of 0.25% and 0.10% HL036 Ophthalmic Solution and placebo using an ANCOVA model that adjust for baseline and site. In addition, the study site by treatment interaction will be explored in a separate model 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% confidence intervals (CIs) for the difference in means and p-values will be reported. Pairwise t-tests from the ANCOVA model will be used to compare treatment and placebo groups. In addition, subjects in either active treatment group will be compared to the placebo group using a separate ANCOVA model.

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 SITE
    MCMC INITIAL = EM;
    VAR BASELINE INFERIOR;
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
- *SITE* is the site id
- *BASELINE* is the baseline pre-CAE® inferior fluorescein staining score in the study eye
- *INFERIOR* is the pre-CAE® inferior fluorescein staining in the study eye at Visit 6 (Day 57 ± 3)

After obtaining twenty complete data sets 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 CHANGE_INFERIOR = 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;

DATA OUTDIFFS;
    SET OUTDIFFS;
    COMPARISON = TREATMENT||' - '||LEFT(_TREATMENT);
RUN;
PROC SORT DATA=OUTDIFFS; BY COMPARISON _IMPUTATION_; RUN;
PROC MIANALYZE DATA=OUTDIFFS;
    BY COMPARISON;
    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® inferior fluorescein staining score in the study eye
- *CHANGE_INFERIOR* is the pre-CAE® inferior fluorescein staining in the study eye at Visit 6 (Day 57 ± 3) – *BASELINE*
- *OUTLS* is the name of the output dataset that contains the statistical results for the treatment means 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 differences in treatment means 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 T-tests.

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 = 386922 OUT = MDATA NIMPUTE = 1
      MINIMUM = 0 MAXIMUM = 4 ROUND = 0.5;
```

```
    MCMC IMPUTE=MONOTONE;
    VAR BASELINE INFERIOR;
RUN;

PROC MI DATA = MDATA SEED = 253464 OUT = OUTDATA NIMPUTE = 20
       MINIMUM = . . 0 0 MAXIMUM = . . 4 4 ROUND = . . 0.5 0.5;
    CLASS SITE TREATMENT;
    MONOTONE REG(INFERIOR = BASE SITE / DETAILS);
    MNAR MODEL(INFERIOR / MODELOBS=(TREATMENT='Placebo'));
    VAR SITE TREATMENT BASELINE INFERIOR;
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
- *SITE* is the site id
- *BASELINE* is the baseline pre-CAE® inferior fluorescein staining score in the study eye
- *INFERIOR* is the pre-CAE® inferior fluorescein staining in the study eye at Visit 6 (Day 57 ± 3)

Analysis of the resulting data will be 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 TREATMENT SITE;
       MODEL CHANGE_INFERIOR = SITE BASELINE TREATMENT / SOLUTION COVB;
       LSMEANS TREATMENT / CL PDIFF;
RUN;
```

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

Pre-CAE® inferior fluorescein staining changes from baseline in the study eye will be displayed graphically in a bar chart with standard error bars by visit and treatment group.

14.1.2 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 [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 each dose of 0.25% and 0.10% HL036 Ophthalmic Solution and placebo using an ANCOVA model that adjust for baseline and site. In addition, the study site by treatment interaction will be explored in a separate model 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% confidence intervals (CIs) for the difference in means and p-values will be reported. Pairwise t-tests from the ANCOVA model will be used to compare treatment and placebo groups. In addition, subjects in either active treatment group will be compared to the placebo group using a separate ANCOVA model. 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 on the ITT population at Visit 6 (Day 57 ± 3). SAS code for the multiple imputation analysis will resemble the code in Section 14.1.1. for pre-CAE® inferior fluorescein staining. 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 sensitivity analyses will include comparisons between treatment and placebo groups using ANCOVA models adjusting for site and baseline and t-tests. Observed data only (ITT and PP) and LOCF analyses will also include Wilcoxon rank sum tests.

Changes from baseline in the pre-CAE® Ocular Discomfort Scale in the study eye will be displayed graphically in a bar chart with standard error bars by visit and treatment group.

14.2 Secondary Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, min and max) by visit and treatment group. Change scores from pre- to post-CAE® will be calculated as post-CAE® score – pre-CAE® score. Changes from baseline will also be summarized descriptively by visit and treatment group. Summaries will also be provided for all subjects in either active treatment group. No imputation will be performed for secondary efficacy variables. Analyses will be performed on the ITT population with observed data only. All exploratory measures will also be presented in subject listings.

The following secondary efficacy endpoints will be tested:

- Fluorescein staining (Ora Calibra® scale); regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score);

- Lissamine green staining (Ora Calibra® scale); regions: inferior, superior, central, temporal, nasal, conjunctival sum);
- TFBUT;
- Conjunctival Redness;
- Unanesthetized Schirmer's Test;
- Ora Calibra® Ocular Discomfort Scale;
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire;
- Visual Analogue Scale;
- OSDI©;
- Ora Calibra® Drop Comfort assessment;
- Daily Diary;
- Tear Mediators

14.2.1 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, 2, 4, 5, and 6. 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.

Pairwise two-sample t-tests will be employed to compare treatment and placebo means 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% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

14.2.2 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, 2, 4, 5, and 6. 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.

Pairwise two-sample t-tests will be employed to compare treatment and placebo means 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% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

14.2.3 TEAR FILM BREAK-UP TIME (TFBUT)

TFBUT will be measured at all scheduled visits on both eyes. Both pre- and post-CAE® assessments will be made at Visits 1, 2, 4, 5, and 6. 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.

TFBUT will be summarized by visit, time point, and treatment group using quantitative summary statistics. Change from baseline will also be summarized.

Pairwise two-sample t-tests will be employed to compare treatment and placebo means 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% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

14.2.4 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, 2, 4, 5, and 6. The conjunctival redness scale ranges from 0 to 4 [redacted].

Scores will be summarized by visit, time point, and treatment group using quantitative summary statistics, including 95% confidence intervals. Change from baseline will also be summarized. Study eye and fellow eye will be summarized separately. Pairwise two-sample t-tests will be employed to compare treatment and placebo means at each visit. Comparisons between treatment groups and between all active groups and placebo will also be conducted. The differences in means, two-sided 95% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

14.2.5 Unanesthetized Schirmer's Test

Unanesthetized Schirmer's Test will be assessed on both eyes post-CAE at Visits 1, 2, 4, 5, and 6. 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 by visit using quantitative summary statistics. Change from baseline will be also summarized.

Pairwise two-sample t-tests will be employed to compare treatment and placebo means at each visit. Comparisons between treatment groups and between all active groups and placebo will also be conducted. The differences in means, two-sided 95% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

14.2.6 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, 2, 4, 5, and 6. 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]

14.2.6.1 ORA CALIBRA® OCULAR DISCOMFORT SCALE PRE-, POST-, AND NON-CAE®

Pre- and post-CAE® assessments of ocular discomfort will be made at Visits 1, 2, 4, 5, and 6. Ocular discomfort will also be assessed during the non-CAE Visit 3. Continuous descriptive statistics, including 95% CIs, as well as changes from baseline will be summarized by treatment group, visit and time point. Pairwise two-sample t-tests will be employed to compare treatment and placebo means 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% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

14.2.6.2 ORA CALIBRA® OCULAR DISCOMFORT SCALE DURING CAE® EXPOSURE

Ocular discomfort scores will be assessed [redacted] during the CAE® exposure. Continuous descriptive statistics, including 95% CIs, as well as changes from baseline will be summarized by

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

14.2.7 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, 2, 4, 5, and 6. 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].

14.2.7.1 ASSESSMENTS DURING VISITS

Ocular discomfort and dry eye symptoms will be summarized by visit, time point, and treatment group using quantitative summary statistics including 95% CIs. Change from baseline will be also summarized. Pairwise 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% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

14.2.7.2 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 day 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. 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 day, time point (morning and evening), and treatment group using quantitative summary statistics including 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. Pairwise two-sample t-tests will be employed to compare treatment and placebo means as well as the changes from baseline at each day 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% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

Daily average scores of ocular discomfort, each individual symptom and worst symptom will be displayed graphically by day in a line plot by treatment group.

14.2.8 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, 2, 4, 5, and 6. 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 95% confidence intervals. Change from baseline will also be summarized.

Pairwise two-sample t-tests will be employed to compare treatment and placebo means 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% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

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

$$\text{OSDI}^{\copyright} = \frac{\text{(sum of scores)} \times 25}{}$$

# of questions answered

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

Pairwise two-sample t-tests will be employed to compare treatment and placebo means at each visit. Comparisons between treatment groups and between all active groups and placebo will also be conducted. The differences in means, two-sided 95% confidence intervals (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 differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. T-tests and Wilcoxon rank sum tests will also be conducted. Analyses will be performed on the ITT population with observed data only.

14.2.10 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 using the Ora Calibra® Drop Comfort Scale. The scale ranges from 0 to 10, with 0 indicating very comfortable and 10 indicating very uncomfortable. Drop comfort will be summarized by time using quantitative summary statistics. Pairwise two-sample t-tests will be employed to compare treatment and placebo means. Comparisons between treatment groups and between all active groups and placebo will also be conducted. The differences in means, two-sided 95% confidence intervals (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.

Descriptions of drop comfort will be assessed at [redacted] following initial dosing at Visit 2 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 will also be summarized by treatment group. Analyses will be performed on the ITT population with observed data only.

14.2.11 Daily Diary

Data from the daily diary and its analysis is described in Section 14.2.7.

14.2.12 Tear Mediators

Analyses of tear mediators will be conducted as ad-hoc analyses. The anticipated ad-hoc analyses of tear mediators are as follows.

Percent change in tear mediators from Visit 2 (Day 1) to Visit 6 (Day 57) will be summarized using continuous descriptive statistics by treatment group. Pairwise two-sample t-tests will be employed to compare treatment and placebo means. Comparisons between treatment groups and between all active groups and placebo will also be conducted. The differences in means, two-sided 95% confidence intervals (CIs) for the difference in means and p-values will be reported. Wilcoxon rank sum tests will also be conducted.

Association between percent change in tear mediators and select efficacy endpoints will be summarized by treatment group and for the active treatment groups combined using Pearson and Spearman correlation coefficients, with 95% confidence intervals constructed using Fisher's Z-transformation. Efficacy endpoints and changes from baseline may also be summarized using continuous descriptive statistics by tertiles of percent change in tear mediators for each treatment group and for the active treatment groups combined. Pairwise comparisons between tertile groups will also be conducted. The differences in means, two-sided 95% confidence intervals (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.

15. Safety Analyses

All safety analyses will be conducted using the Safety population.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an investigational product (IP) in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (eg, 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 (eg, off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (eg, anatomical limitations), and therapeutic parameters (eg, energy applied, sizing, dose release) associated with medical device. All AEs will be coded using MedDRA Version 20.1.

Treatment-emergent adverse events (TEAEs) are defined as any adverse event that occurs or worsens after the first dose of study treatment. AEs recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

An overall summary will be presented that includes the number of AEs, TEAEs, serious AEs (SAE), and serious TEAEs (TE-SAE). 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. The summary will also include 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. The occurrence of non-ocular and ocular TEAEs will also be tabulated by SOC, PT, and maximal severity, as well as by study day of onset (prior to Day 9, Day 9 to Day 29, After Day 29).

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

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

Severity of an adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by the investigator or reported to him/her by the patient/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 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.
- *Unclassified:* When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

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

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 AEs leading to study discontinuation, AEs leading to death and SAEs.

15.2 Best-Corrected Visual Acuity (ETDRS)

The visual acuity procedure will be performed at each visit pre-CAE®. The logarithm of the minimum angle of resolution (logMAR) VA must be assessed using an 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.

15.3 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, 2, 4, 5, and 6. 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 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.

15.4 Dilated Fundoscopy Examination

A dilated fundoscopy exam will be performed during the study post-CAE® at Visits 1 and 6, and potentially at an Early Termination Visit. Observations will be graded as Normal or Abnormal NCS or Abnormal CS. Abnormal findings will be described. The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve

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 undilated fundoscopy parameters will also be provided comparing Visit 6 to baseline (Visit 1). A subject listing of the undilated fundoscopy parameters will also be produced.

15.5 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 and 6, and potentially at an Early Termination Visit. 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.

15.6 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 patients with anti-drug antibodies (ADA) will be presented by visit and treatment group. Exact 95% Clopper-Pearson confidence intervals 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 patients 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% confidence intervals (CIs) for the difference in means and p-values will be reported. Wilcoxon rank sum tests will also be conducted.

16. Interim Analyses

There will be no interim analyses in this study.

17. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

18. Revision History

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

19. Tables

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

Table Number	Title	Population

Table Number	Title	Population
TABLE 14.1.1	**SUBJECT DISPOSITION**	**ALL ENROLLED SUBJECTS**
TABLE 14.1.2.1	**DEMOGRAPHICS ITT POPULATION**	**ITT**
TABLE 14.1.2.2	DEMOGRAPHICS SAFETY POPULATION	SAFETY
TABLE 14.1.3.1	BASELINE DISEASE CHARACTERISTICS (STUDY EYE)	ITT
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 14.2.1.1	**PRE-CAE® INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA® SCALE)**	**ITT WITH MCMC**
TABLE 14.2.1.2	**PRE-CAE® INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA® SCALE)**	**ITT WITH OBSERVED DATA ONLY**
TABLE 14.2.1.3	PRE-CAE® INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA® SCALE)	ITT WITH LOCF
TABLE 14.2.1.4	PRE-CAE® INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA® SCALE)	ITT WITH PMM
TABLE 14.2.1.5	PRE-CAE® INFERIOR CORNEAL FLUORESCEIN STAINING (ORA CALIBRA® SCALE)	PP WITH OBSERVED DATA ONLY
TABLE 14.2.2.1	**PRE-CAE® OCULAR DISCOMFORT (ORA CALIBRA® SCALE)**	**ITT WITH MCMC**
TABLE 14.2.2.2	**PRE-CAE® OCULAR DISCOMFORT (ORA CALIBRA® SCALE)**	**ITT WITH OBSERVED DATA ONLY**

Table Number	Title	Population
TABLE 14.2.2.3	PRE-CAE® OCULAR DISCOMFORT (ORA CALIBRA® SCALE)	ITT WITH LOCF
TABLE 14.2.2.4	PRE-CAE® OCULAR DISCOMFORT (ORA CALIBRA® SCALE)	ITT WITH PMM
TABLE 14.2.2.5	PRE-CAE® OCULAR DISCOMFORT (ORA CALIBRA® SCALE)	PP WITH OBSERVED DATA ONLY
TABLE 14.2.3.1	FLUORESCEIN CORNEAL AND CONJUNCTIVAL STAINING (ORA CALIBRA® SCALE)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.2	LISSAMINE GREEN CORNEAL AND CONJUNCTIVAL STAINING (ORA CALIBRA® SCALE)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.3	TEAR FILM BREAK-UP TIME	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.4	ORA CALIBRA® CONJUNCTIVAL REDNESS SCALE FOR DRY EYE	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.5	UNANESTHETIZED SCHIRMER'S TEST	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.6	ORA CALIBRA® OCULAR DISCOMFORT SCALE	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.7	ORA CALIBRA® OCULAR DISCOMFORT SCALE (DURING CAE®)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.8	ORA CALIBRA® OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE	ITT WITH OBSERVED DATA ONLY

Table Number	Title	Population
TABLE 14.2.3.9	ORA CALIBRA® OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE FOR DRY EYE (DIARY)	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.10	VISUAL ANALOGUE SCALE	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.11	OCULAR SURFACE DISEASE INDEX (OSDI)©	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.12	ORA CALIBRA® DROP COMFORT SCALE	ITT WITH OBSERVED DATA ONLY
TABLE 14.2.3.13	ORA CALIBRA® DROP COMFORT QUESTIONNAIRE	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 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	SAFETY

Table Number	Title	Population
	EVENTS BY MAXIMAL SEVERITY	
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	BEST CORRECTED 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

20. 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 Number	Title
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 STUDY MEDICATION INSTILLATION
LISTING 16.2.5.2	STUDY DRUG EXPOSURE AND DOSING COMPLIANCE
LISTING 16.2.5.3	STUDY DRUG ACCOUNTABILITY
LISTING 16.2.5.4	URINE PREGNANCY TEST
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	TEAR FILM BREAK-UP TIME (TFBUT)
LISTING 16.2.6.4	CONJUNCTIVAL REDNESS
LISTING 16.2.6.5	UNANESTHETIZED SCHIRMER'S TEST
LISTING 16.2.6.6	ORA CALIBRA® OCULAR DISCOMFORT SCALE
LISTING 16.2.6.7	ORA CALIBRA® OCULAR DISCOMFORT SCALE (DURING CAE)
LISTING 16.2.6.8	ORA CALIBRA® OCULAR DISCOMFORT & 4-SYMPTOM QUESTIONNAIRE
LISTING 16.2.6.9	OCULAR DISCOMFORT AND DRY EYE SYMPTOMS REPORTED IN THE SUBJECT DIARY
LISTING 16.2.6.10	VISUAL ANALOGUE SCALE
LISTING 16.2.6.11	OCULAR SURFACE DISEASE INDEX (OSDI)©
LISTING 16.2.6.12	ORA CALIBRA® DROP COMFORT SCALE
LISTING 16.2.6.13	ORA CALIBRA® DROP COMFORT QUESTIONNAIRE
LISTING 16.2.6.14	TEAR COLLECTION
LISTING 16.2.7.1	ALL ADVERSE EVENTS
LISTING 16.2.7.2	SERIOUS ADVERSE EVENTS

Listing Number	Title
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	BEST-CORRECTED 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

21. Figures

Figure Number	Title	Population
FIGURE 14.2.1.1	**PRE-CAE® INFERIOR 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	DAILY AVERAGE DIARY SCORES	ITT WITH OBSERVED DATA ONLY