Statistical Analysis Plan

Official title：	**A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of HBM9036 Ophthalmic Solution 0.25% versus Placebo in Subjects with Moderate to Severe Dry Eye**
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Statistical Analysis Plan

Study No.:	9036.1
Protocol Title:	A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of HBM9036 Ophthalmic Solution 0.25% versus Placebo in Subjects with Moderate to Severe Dry Eye
Clinical Phase:	Phase 2
Countries and sites:	**China**
Investigational Product(s) Name:	HBM9036 Ophthalmic Solution

Sponsor Information

Sponsor	Harbour BioMed (Guangzhou) Co., Ltd

Confidentiality Statement

Approval Signatures

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List of Abbreviations

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
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
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
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
OSDI	Ocular Surface Disease Index
PP	Per Protocol
PT	Preferred Term
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	Treatment-Emergent Serious 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 HBM9036. Samples reporting tables, figures, and listing (TFL) can be found in a separate document (TFL shells, to be named).

1.1 Study Objectives and Endpoints

The objectives of this study are to compare the safety and efficacy of 0.25% HBM9036 Ophthalmic Solutions to placebo for the treatment of the signs and symptoms of moderate to severe dry eye.

The primary objective is to evaluate the efficacy of 8-week continuous treatment with HBM9036 ophthalmic solution (BID) in Chinese patients with moderate and severe dry eye and to provide information for the Phase III trial decision.

The primary efficacy endpoint is:

- The change from baseline in change from pre- to post-CAE® inferior corneal staining score (ICSS) of the study eye evaluated at Visit 6 (Day 57, Week 8) according to Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale (Referred to as ΔΔICSS at Day 57)

Secondary efficacy endpoints are:

- ΔΔICSS at Visit 5 (Day 29)
- The change from baseline in pre-CAE® ocular discomfort of the study eye evaluated at Visit 6 according to Ora Calibra® Ocular Discomfort Scale
- The change from baseline in pre-CAE® ocular discomfort of the study eye evaluated at Visit 5 according to Ora Calibra® Ocular Discomfort Scale
- The change from baseline in pre-CAE® symptom score evaluated at Visit 6 according to Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- The change from baseline in pre-CAE® symptom score evaluated at Visit 5 according to Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- The change from baseline in post-CAE® TFBUT© of the study eye evaluated at Visit 6
- The change from baseline in post-CAE® conjunctival redness score of the study eye evaluated at Visit 6 according to Ora Calibra® Conjunctival Redness Scale

- The change from baseline in Schirmer's test results at Visit 6
- The changes from baseline in OSDI© scores at Visit 6
- The change from baseline in pre-CAE® burning sensation score evaluated at Visit 6 according to Visual Analogue Scale (VAS)
- The change from baseline in average weekly burning sensation score in subject diary at Week 8

1.2 Study Design

This is a multi-center, randomized, double blind, placebo control study. One hundred (100) study subjects are randomly assigned to either HBM9036 or placebo group in a 1:1 ratio. Randomized study subjects receive the first dose of study drug on the randomization day (referred to Day 1). Study subjects receive 8 weeks of study drug treatments. Study subjects return to the office on Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 5), and Day 57 (Visit 6) for efficacy and safety assessments. The End of Study (EoS) is a telephone safety follow-up 7 days after the last dose of study drug. More details can be found in the study protocol.

1.3 Statistical Hypotheses for Trial Objectives

The statistical hypothesis of this study is:

H_0: There is no difference between HBM9036 ophthalmic solution (0.25%) and placebo in the change from baseline of the change from pre- to post-CAE® ICSS of the study eye at Visit 6 (Day 57， Week 8), according to Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale.

H_1: The change from baseline of the change from pre- to post-CAE® ICSS of the study eye at Visit 6 (Day 57， Week 8) using the Ora Calibra® scale is different with HBM9036 ophthalmic solution (0.25%) from with placebo.

1.4 Sample Size Justification

This study plans to enroll 50 subjects in each treatment group so a total of 100 subjects will be randomized. Assuming a 20% drop out rate, 40 subjects per group are expected to complete the study.

The treatment effect is of little clinical relevance if the difference between HBM9036 and placebo in the primary endpoint is greater than -0.1. In contrast, if the difference is -0.3 or less, it is considered of clinical significance and a Go decision to phase 3 will be likely.

If the difference is between -0.3 and -0.1, a decision will be made based on other data, e.g., efficacy in secondary endpoints and safety data.

The sample size is determined based on the probability of making a correct decision given the true effect size (i.e., efficacy scenario). Assuming the standard deviation is 0.7 unit, Table 1 below presents the summary of probabilities for observing the efficacy.

Table 1. Probability of making a Go, Pending, or No-Go decision, given various true effect size in ΔΔICSS.

True ΔΔICSS	Observed ΔΔICSS <= -0.3 (Go Decision)	Observed ΔΔICSS between -0.3 and -0.1 (Pending Decision)	Observed ΔΔICSS > -0.1 (No-Go Decision)
0.0	*3.0%*	*23.3%*	*73.8%*
0.1	*9.9%*	*40.1%*	*50.0%*
0.2	*26.2%*	*48.6%*	*25.2%*
0.3	*50.0%*	*40.2%*	*9.8%*
0.4	*74.8%*	*22.7%*	*2.6%*

1.5 Randomization and Blinding

This study is a randomized, double-blinded, placebo-controlled, parallel-group Phase II study. Eligible study subjects are randomly assigned to HBM9036 or placebo group at a 1:1 ratio.

Subjects receive either HBM9036 Ophthalmic Solution (0.25%) or placebo solution as topical ophthalmic drops (at the ratio of 1:1) administered bilaterally BID. Subjects, Sponsor, CRO and site personnel are masked to treatment assignment.

2. General Analysis Definitions

2.1 Visit Windows

Subjects will be followed up for 8 weeks according to the study protocol. Table 2 summarizes planned office visits and analysis time window. Clinical assessments will be analyzed based on their study days when the assessments are performed, not based on the visit label in the database. Definition of visit time interval for the analysis purpose is provided in table 2.

Table 2. Summary of study visits according to the study protocol and this statistical analysis plan

Scheduled Visit	Timepoint label (Target day)	Scheduled Visit Window	Analysis Window*
Visit 1	Day-14	± 2 Days	Day -1 and before
Visit 2	Day 1	NA	Day 1
Visit 3	Day 8	± 1 Day	Day 2 to 12
Visit 4	Day 15	± 2 Days	Day 13 to 21
Visit 5	Day 29	± 2 Days	Day 22 to 42
Visit 6	Day 57	± 3 Days	Day 43 and after

*If there are more than 1 measure within the analysis window. The measure with the closest to the target day will be selected. If there are ties, the measure that are after the target day will be selected. If there are more than 1 measure on the same day, the average of these measures will be used. For descriptive result of endpoint like Abnormal or Normal, if there are more than 1 measure on the same day, and if the results are different, the Abnormal will be used.

2.2 Definition of Study Dates

For each study subject,

- First dose date = the date on which the first dose of study drug is taken by the subject. If it is missing or incomplete, it is set to the earliest logically possible date on or after randomization.
- Last dose date = the date on which the last dose of study drug is taken by the subject. If it is missing or incomplete, it is set to the latest logically possible date recorded in diary.

2.3 Analysis Sets

Full Analysis Set (FAS)

The full analysis set includes all the randomized subjects who have received at least one dose of study drug (including placebo) according to the principle of intention-to-treat (ITT). Subjects will be analyzed as randomized.

Per Protocol Set (PPS)

The PP set is a subset of FAS, including subjects who do not have protocol deviations or events that will significantly affect efficacy assessments. Protocol deviations will be assessed and subjects who will be excluded from PPS will be identified and documented prior to database lock.

Safety Set (SS)

The safety set 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. The actual treatment arm will be defined by first drug dosing group. The SS will be used for analysis of laboratory examination data, adverse events, and adverse reactions.

2.4 Definition of Subgroups

The four subgroups below are considered for subgroup analyses of primary efficacy outcome：

- Baseline pre-CAE® inferior corneal staining score <2, ≥2；
- Baseline conjunctival redness score <2, ≥2；
- Duration of dry eye disease (<average level (year) ≥ average level (year));
- Time to qualify during CAE® at Visit 2 (<20 minutes or ≥20 minutes)

The subgroup analyses above will be performed for secondary efficacy outcomes like pre to post-CAE® ICSS, pre-CAE® ODS, VAS(Burning) and Diary. To determine who get qualified study eye for ODS at Visit 2 within 20 minutes vs. after 20 minutes as defined by:
Reporting an Ocular Discomfort score ≥3 at 2 or more consecutive time points in at least the study eye during CAE® exposure (if a subject has an Ocular Discomfort rating of 3 at time = 0 for an eye, he/she must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye). Note: a subject cannot have an Ocular Discomfort score of 4 at time = 0).

Duration of dry eye disease will be defined by informed consent date (only year) − diagnosis date (only year). If diagnosis date is 2019, the duration will be 1. All subgroup analysis will base on study eye and PPS.

2.5 Study Day and Relative Day

Study Day 1 or Day 1 refers to the day of randomization [the start of the first study agent administration]. All efficacy and safety assessments at all visits will be assigned a day relative to this day.

Study day is defined as:

- Day on or after Day 1: Date – (date of Day 1) + 1;
- Day before Day 1: Date – (date of Day 1).

2.6 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 pair. For the non-CAE® Visit 3 and Visit 4, 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 at Visit 2. For measures from daily subject diaries, baseline is defined as the average of all days during the run-in period. For some safety endpoints like IOP, Fundus photography/Dilated fundoscopy and Slit-Lamp Biomicroscopy Examination, baseline will be the last non-missing measure prior to the initiation of run-in placebo, usually at Visit 1. For BCVA, baseline will be the last non-missing measure prior to the initiation of study treatment, usually at Visit 2. Change from baseline will be calculated as follow-up visit minus baseline value. In this study, the baseline data analysis will be based on the full analysis set (FAS).

3. Subject Disposition

3.1 Disposition

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. Disposition will be summarized by treatment group and for all subjects.
The number of randomized subjects in each of the analysis populations (FAS, PPS and SS) will be displayed by treatment. 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 including: AE, subject choice, etc. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

3.2 Protocol Deviations

The number and percentage of subjects with any protocol deviations will be summarized by treatment group for all randomized subjects. 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 FAS, PPS, and SS populations. In addition, subjects who will be excluded

from PP will be identified prior to database lock. Reasons of exclusion will be provided in a listing.

4. Demographics and Baseline Characteristics

4.1 Demographics

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 FAS.

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 (take the floor value as an integer)

If the date of birth is partially missing for days in eCRF, 15th will be used for imputation.

Because the study is conducted in China. The vast majority of study subjects, if not all, is expected to be Chinese. Therefore, a summary of race and ethnics, as well as eye colors and other demographics that are almost no variation among Chinese will not be provided to streamline the study report. If there are non-Chinese subjects. Race/ethnics and other race/ethnics related demographics will be provided in a listing.

4.2 Baseline Disease Characteristics

Baseline disease characteristics will be summarized by treatment group using continuous descriptive statistics for pre-CAE® to post-CAE® Inferior Corneal Staining Score (ICSS), pre-CAE® Ora Calibra® Ocular Discomfort Scale (ODS), total OSDI© score, post-CAE® TFBUT, Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire, Ora Calibra® Conjunctival Redness Scale, unanesthetized Schirmer's test, Visual Analogue Scale (VAS), BCVA, IOP and others.

4.3 Medical History

Medical history will be coded using MedDRA Version 22.

Ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject by System Organ Class (SOC) and Preferred Term (PT) using the FAS population. Non-ocular medical history will be similarly summarized at the subject. If a subject reported the same PT multiple times within the

same SOC, that PT will only be reported once within that SOC. Listings of medical history will be generated separately for ocular and non-ocular data.

5. Treatments and Medications

5.1 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using WHO Drug Global Dictionary March 2019 and summarized to the therapeutic drug class according to Anatomical Therapeutic Chemical (ATC) 4 classification and preferred name. Prior medications are defined as any therapy used and stopped before the first day of run-in period. Concomitant medications are defined as any therapy used on or after the first day of run-in period, including those that started before and continue after the start of the first day of run-in period.

Prior and concomitant medications will be summarized separately using the FAS population. 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 one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated separately for ocular and non-ocular data.

5.2 Study Treatments

5.2.1 Extent of 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 first drug dosing + 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 first drug dosing + 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.

5.2.2 Treatment 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 on 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 by week will be calculated from the number of used vials on the drug accountability case report form (CRF). The number of doses taken in total will be calculated from the number of drug administered in diary. The planned drug use is calculated as (daily drug use specified in the protocol) × (the number of days between the 2 study visits). 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 × (the Study Day of the last dose - the Study Day of the first dose +1) if discontinued, and 2 × (the Study Day of the visit 6 - the Study Day of the first dose) if completed 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.

6. Efficacy Analysis

6.1 Analysis Specifications

6.1.1 Level of Significance

All statistical testing 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".

6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is inferior corneal staining (sign), Pre- to Post-CAE at Day 57.

6.2.1 Definition

For the primary efficacy endpoint, the pre- to post-CAE® ICSS change will be calculated as post-CAE® ICSS– pre-CAE® ICSS, noted as ΔICSS. The change from baseline in ΔICSS will be calculated as visit (ΔICSS) – baseline (ΔICSS) (denoted as ΔΔICSS). Treatment comparisons between treatment and placebo groups will be calculated as treatment – placebo (denoted as ΔΔΔICSS). A negative value indicates a better outcome for the treatment group (i.e., the treatment group increase more or worsen less in dry eye signs or symptoms than the placebo group).

6.2.2 Analysis Methods

An ANCOVA model will be used to compare ΔΔICSS at Day 57 (Visit 6) (measured by the Ora Calibra® scale), between HBM9036 and placebo. The ANCOVA model will include treatment and baseline ΔICSS as the only 2 covariates. The between-group differences in ΔΔICSS, two-sided 95% confidence intervals (CIs), and p-value will be reported.

Two-sample t-test will be conducted as a sensitivity analysis.

The primary analysis will be performed on the PP populations. After obtaining data sets and calculating changes from baseline, the following SAS code will be used to run the ANCOVA model on data sets:

```
PROC MIXED DATA = OUTDATA;
  CLASS TREATMENT;
  MODEL CHANGE_INFERIOR = BASELINE TREATMENT / SOLUTION COVB;
  LSMEANS TREATMENT / CL PDIFF;
  ODS OUTPUT LSMEANS = OUTLS DIFFS = OUTDIFFS;
RUN;
```

where

- *TREATMENT* is the name of the treatment group variable
- *BASELINE* is the baseline post-CAE® – pre-CAE® inferior corneal staining score in the study eye
- *CHANGE_INFERIOR* is the post-CAE® – pre-CAE® inferior corneal staining score in the study eye at Visit 6 (Day 57 ± 3) – *BASELINE*

Sensitivity analyses will be performed:

- on the FAS population using the last observation carried forward (LOCF) - imputation method for missing values will be used which means the last value from the previous visits will be carried forward, matching pre-CAE® or post-CAE® time points and a pre-CAE® time point will never be imputed for a post-CAE® value, and vice versa to have a full accounting of the FAS at the Day 57
- on the FAS using MMRM methodology

An example of the SAS code implementation of the ANCOVA model for the FAS population using LOCF is as follows:

```
PROC MIXED;
        CLASS TREATMENT;
        MODEL CHANGE_INFERIOR = BASELINE TREATMENT / SOLUTION COVB;
        LSMEANS TREATMENT / CL PDIFF;
RUN;
```

For LOCF, baseline value will be used for post baseline if both visit 5 and visit 6 are missing.

An example of the SAS code implementation of the ANCOVA model for the MMRM is as follows:

```
PROC MIXED;
        CLASS TREATMENT PTNO VISIT;
        MODEL CHANGE_INFERIOR = BASELINE TREATMENT VISIT VISIT*BAELINE
VISIT*TREATMENT/ DDFM=KR SOLUTION CHISQ;
        REPEATED VISIT/SUBJICT=PTNO TYPE=UN R RCORR;
        LSMEANS TREATMENT*VISIT / PDIFF=ALL OM CL ALPHA=0.05 SLICE=VISIT;
RUN;
```

where

- *PTNO* is Patient number (ID)
- *VISIT* is visit timepoint (5, 6)
- *VISIT*BAELINE* is the Visit*Baseline interaction term
- *VISIT*TREATMENT* is the Visit*Treatment interaction term

Mean changes from baseline will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, visit and treatment-by-visit interaction, as well as the continuous,

fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance structure will be used to model the within-patient measurement.

If a patient misses a visit, the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption.

Pre-CAE® to post-CAE® inferior corneal staining changes from baseline in the study eye will be displayed graphically by day and visit in a line plot by treatment group.

6.3 Secondary Efficacy Endpoints

Continuous and ordinal secondary efficacy variables collected at the specific visit will be summarized descriptively (n, mean, standard deviation, median, min and max). Change scores from pre- to post-CAE® will be calculated as post-CAE® – pre-CAE® score. The change from baseline will be calculated as visit – baseline. Two-sample t test and an ANCOVA model adjusting for baseline will also be assessed where appropriate. No imputation will be performed for secondary efficacy endpoints.

Tear film break-up time (TFBUT), conjunctival redness score, unanesthetized schirmer's test result, ocular discomfort scale and visual analogue scale will be summarized by visit, time point, and treatment group using quantitative summary statistics. Changes from baseline will be compared between treatment groups using ANCOVA model that adjust for baseline. The differences in means, two-sided 95% confidence intervals (CIs) for the difference in means will be reported. Analyses will be performed on the PP population with observed data only.

Ocular discomfort and dry eye symptoms will be recorded by both visit and daily diary. For visit summary, quantitative summary statistics will be used as above. For diary summary, the average of the morning and evening assessments will be calculated for each day and symptom. Changes from baseline in weekly average scores at week 8 will be compared between treatment groups using ANCOVA model that adjust for baseline. The differences in means, two-sided 95% confidence intervals (CIs) for the difference in means will be reported. Analyses will be performed on the PP population with observed data only. Changes from baseline in weekly average scores of ocular discomfort, each individual symptom will be displayed graphically by week in a line plot by treatment group.

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability.

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 95% CIs, as well as changes from baseline will be summarized by treatment group and visit.

Changes from baseline in total OSDI© score will be compared between treatment groups using ANCOVA model that adjust for baseline. The differences in means, two-sided 95% confidence intervals (CIs) for the difference in means will be reported. Analyses will be performed on the PP population with observed data only.

7. Safety Analysis

Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Authorities (MedDRA). Summary will focus on treatment-emergent AE (TEAE), which is defined as AE that occur or worsen after the first dose of study treatment. Frequencies and percentages of subjects with TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term.

7.1 Adverse Event

An overall summary will be presented that includes the number of AEs, serious AEs (SAE), TEAEs 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 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. 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. All AEs will be coded using MedDRA Version 22.

Treatment-emergent adverse events (TEAEs) are defined as any adverse event that occurs or worsens from the first dose of study treatment (at visit 2) to last dose+7 day. 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 level by SOC and PT. Ocular TEAEs will also 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. In the summary, SOC will be listed in order of descending frequency by study active treatment 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.

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. 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. All probable, unclassified, and definite TEAEs are considered as treatment-related TEAEs. All AEs will be presented in a subject listing.

7.2 Other Safety Endpoints

Best-Corrected Visual Acuity (ETDRS)

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.

Slit-Lamp Biomicroscopy Examination

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.

Ora Calibra® Drop Comfort Assessment

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 SS.

Intraocular Pressure (IOP)

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.

Fundus photography/dilated fundoscopy

The following examinations are done in the study:

- 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.