STATISTICAL ANALYSIS PLAN

PROTOCOL: SDP-4-CS201

A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group, Dose-Response Study of SDP-4 Ophthalmic Solution in Subjects with Dry Eye Disease (DED)

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AMEMDMENT HISTORY

None

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
BCVA	best-corrected visual acuity
BID	twice daily
CSR	clinical study report
DED	dry eye disease
eCRF	electronic case report form
IOP	Intraocular Pressure
IP	investigational product
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NE	Non-Study Eye
OD	right eye
OS	left eye
OU	both eyes
PP	Per Protocol
PT	Preferred Term
SAE	Serious adverse event
SAF	Safety Population
SANDE	Symptom Assessment in Dry Eye
SAP	statistical analysis plan
SCRN	Screened Population
SD	standard deviation
SE	Study Eye
SOC	System Organ Class
SUD	single-use dose
TBUT	tear break-up time
TEAE	Treatment-emergent AEs
TFLs	Tables, Figures, and Listings
VAS	visual analogue scale
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the final statistical analysis for subject information, efficacy data, and safety data to be done for the study entitled "A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group, Dose-Response Study of SDP-4 Ophthalmic Solution in Subjects with Dry Eye Disease (DED)" (Date Amendment 1: 03APR2019). Mock shells are also produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to finalized SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report (CSR) contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the CSR.

1.1 Study Objectives

The primary objective of this study is to assess the safety and efficacy of SDP-4 Ophthalmic Solution in subjects with DED over a 12-week (84-day) treatment period.

1.2 Study Design

This is a Phase 2, multicenter, double-masked, randomized, vehicle-controlled, dose-response, parallel-group study designed to evaluate the ocular and systemic safety and efficacy of SDP-4 ophthalmic solution in subjects with moderate to severe DED in both eyes (OU) over a 12-week (84-day) treatment period.

Subjects will be randomized to 1 of 3 concentrations (0.1%, 1.0% and 3.0%) of SDP-4 Ophthalmic Solution or vehicle in a 1:1:1:1 ratio, with 75 subjects randomized to each group in parallel. All investigational products (IP) (SDP-4 concentrations and vehicle) will be provided in single-use dose (SUD) containers seal packed into foil pouches.

The IP will be administered via topical ocular instillation, one drop per eye, twice daily (BID) for 12 weeks (84 days). Both eyes will be treated. A 2-week screening/run-in period on BID vehicle will precede the 12-week randomized treatment period.

Subjects must have a Symptom Assessment in Dry Eye (SANDE) total score of ≥ 40 at Visit 1/Screening and Visit 2/Day 1 to enter the trial. The study will consist of 7 clinic visits, 2 visits during the screening period and 5 on treatment visits: Visit 1 (Day -14 ± 2/Screening Visit), followed by a 2-week run-in on BID vehicle, Visit 2 (Day 1/Confirmatory and Randomization Visit), Visit 3 (Day 7 ± 2), Visit 4 (Day 14 ± 2), Visit 5 (Day 28 ± 2), Visit 6 (Day 56 ± 4) and Visit 7 (Day 84 ± 4/End of Study Assessments).

If a subject complains of persistent dry eye symptoms, the site may provide the subject with unpreserved artificial tears (provided by the Sponsor), to be used

only if necessary. The subject must return all used and unused artificial tears at each visit so the site can conduct accountability to assess the use of artificial tears. Artificial tears may not be used within 2 hours prior to any study visit.

1.3 Sample Size Estimation

A sample size of 70 subjects per treatment group will have 80% power to detect a treatment difference of 11.7 units in SANDE total score and 1.2 seconds in TBUT at Visit 7/Day 84 using a t-test with a 0.05 two-sided significance level. This calculation is based on the assumptions shown in Table 1. Sample size was derived using assumptions based on expected SANDE and TBUT values, TBUT being one of several secondary outcomes to be analyzed. Over-enrollment of 5 subjects per group/20 subjects per study is planned to account for discontinuations.

Table 1. Sample Size Estimation

Assumptions	SANDE	TBUT
Test significance level, α	0.050	0.050
1 or 2 sided test	2	2
Difference in means, $\mu_1 - \mu_2$	11.684	1.192
Common standard deviation	24.500	2.500
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert/\sigma$	0.477	0.477
Power (%)	80	80
n per group	70	70

1.4 Randomization and Masking

Subjects will be randomized in a 1:1:1:1 ratio to 0.1%, 1.0% or 3.0% SDP-4 Ophthalmic Solution or vehicle in parallel groups. A randomization code for allocating the treatment groups will be prepared by an independent unmasked biostatistician not involved in the day-to-day running of the study. If subjects meet eligibility criteria at Screening (Visit 1/Day -14) and Visit 2/Day 1, subjects will be randomly assigned to investigational product (IP) at Visit 2. Clinical sites will utilize the Interactive Web Response System (IWRS) to randomize and assign kits to subjects. The assigned subject randomization number and IP kit numbers will be recorded in the subject's electronic case report form (eCRF). All SDP-4 concentrations and vehicle will be dispensed in one-month supplies at Visits 2, 5, and 6.

The study will be double-masked. Subjects, the Investigator, and all site personnel responsible for performing study assessments will remain masked to treatment assignment.

Should it be necessary to unmask a subject's treatment assignment in case of emergency, the Investigator may obtain the treatment code for a given randomized subject from the IWRS. The treatment code is to be obtained only if a medical emergency exists and knowledge of the medication being taken will influence the medical management of the subject.

1.5 Planned Interim Analysis

No interim analyses are planned.

1.6 Criteria for Evaluations Defined in Protocol:

1.6.1 Screen Failures

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria or met at least 1 of the exclusion criteria, and has not been randomized into the study. Based on Investigator discretion and Sponsor approval, subjects who initially failed to meet the inclusion/exclusion criteria may be rescreened at a later time if their eligibility status has changed. The subject will retain the same subject identification number that he/she was assigned at the first screening.

1.6.2 Demographics and Background Characteristics

Demographic information including age, gender, race, ethnicity, and date of informed consent will be recorded. Clinically significant medical and ocular history will be documented and will include any previously diagnosed ocular abnormalities and ocular surgeries, including laser and non-laser procedures. All current medications (prescription and over-the-counter) taken at Screening, 90 days prior to Screening, and throughout the course of the study will be recorded. Information regarding the dates of first and last dose, site of dosing (e.g., right eye (OD), left eye (OS), both eyes (OU), systemic), and the reason the medication is being taken must be recorded in the eCRF. A urine pregnancy test will be performed at Visit 1/Screening and Visit 2/Day 1 and repeated at Visit 7/Day 84 or the Early Discontinuation Visit for women of childbearing potential only.

1.6.3 Treatment Compliance

The amount of used and unused run-in vehicle returned at Visit 2/Day 1 and used and unused randomized IP returned at Visit 5/Day 28, Visit 6/Day 56, and Visit 7/Day 84 will be documented by site personnel and captured on eCRF to be used should the need arise. Additionally, the amount of used and unused artificial tears will be documented by site personnel starting at Visit 2 through Visit 7 if the artificial tears were required by the subject.

1.6.4 Efficacy Assessments

Efficacy will be measured by assessment of DED symptoms and signs. More details are described in the following table.

Table 2. Summary of Efficacy Assessments

Assessment	Measurements	Visits
SANDE questionnaire	• Frequency of symptoms: 0-100 (Rarely – All the time) • Severity of symptoms: 0-100 (Very mild – Very severe) • Total score, captured by eCRF calculated as the square root of the frequency score times the square root of the severity score: 0 - 100	All
Individual dry eye symptoms rated on a visual analogue scale (VAS)	• Itching: 0-100 (Doesn't itch at all – Want to scratch my eyes out) • Foreign Body Sensation: 0-100 (Don't feel like I have something in my eye – Feel like I have sand in my eye) • Burning/Stinging: 0-100 (Doesn't burn/sting at all – Severe) • Fluctuating Vision: 0-100 (Vision is fine – Vision constantly changes) • Eye Dryness: 0-100 (Not dry at all – Extremely dry) • Eye Discomfort: 0-100 (Very comfortable – Extremely uncomfortable) • Photophobia: 0-100 (Not sensitive to light – Extremely sensitive to light) • Eye Pain: 0-100 (No eye pain – Need pain medicine)	Days 1, 7, 14, 28, 56, 84
Tear break-up time (seconds)	The procedure is conducted 2 times for each eye. The calculated average for each eye will be captured by eCRF.	All
Corneal fluorescein staining	• Each of the 5 areas (central, superior, temporal, nasal, inferior) of the cornea, graded on a 0-3 scale • Total summed per eye: 0 - 15	All
Slit-lamp examination	Conjunctival hyperemia, graded to 6 levels based on McMonnies photographic scale (0 – 5)	All

Conjunctival Lissamine Green Staining	• Each of the 6 areas (Zone 1: temporal/canthal, Zone 2: superior mid-temporal, Zone 3: inferior mid-temporal, Zone 4: superior mid-nasal, Zone 5: inferior mid-nasal, Zone 6: nasal/canthal) of the conjunctiva, graded on a 0-3 scale for each eye • Total summed per eye, excluding superior zones 2 and 4: 0 - 12	All
Anesthetized Schirmer's Test (mm)	Following instillation of topical anesthetic, filter paper strips will be placed in both eyes inside the lower eyelid (conjunctival sac) at the same time. The eyes are closed for 5 minutes. The paper is then removed and the amount of moisture on each strip in millimeters (mm) is measured.	Screening, Days 1, 84

1.6.5 Safety

Safety assessments will include monitoring of adverse events (AEs), best-corrected visual acuity (BCVA), slit-lamp examination, dilated fundus examination and intraocular pressure.

More details are described in following table.

Table 3. Summary of Safety Assessments

Assessment	Measurements	Visits
Adverse Events	• AE term (verbatim and MedDRA preferred term and system organ class) • Location (OD, OS, OU, Non-Ocular) • Onset (date) • Resolution (date) • Severity grade (mild, moderate, severe) • Relationship to IP (not suspected, suspected) • Action taken (none, IP temporarily interrupted, IP permanently discontinued; concomitant medication taken; hospitalization/prolonged hospitalization; other) • Serious outcome (yes/no)	All
Best-Corrected Visual Acuity	logMAR per eye	All

Slit-lamp examination	Results, abnormal findings, and clinical significance of abnormal findings for following anterior ocular structures: • Lid (negative, positive): erythema (0-3, CS/NCS), edema (0-3, CS/NCS), other (CS/NCS) • Conjunctiva (negative, positive): edema (0-3, CS/NCS), other (CS/NCS • Cornea (negative, positive): edema (0-3, CS/NCS), other (CS/NCS) • Anterior chamber (negative, positive): cells (0-4, CS/NCS), flare (0-4, CS/NCS), other (CS/NCS) • Iris/Pupil (negative, positive): other (CS/NCS) • Lens status (phakic, pseudophakic, aphakic): lens opacity (0-4, CS/NCS) if phakic, posterior capsule opacity (clear, open, clouding, CS/NCS) if pseudophakic	All
Dilated Fundus Exam	Results (normal, abnormal NCS, abnormal CS, not done) and abnormal findings for following ocular structures: • Vitreous • Peripheral retina • Macula • Optic nerve • Cup-to-disc ratio	Screening, Day 84
Intraocular Pressure Measurement (mmHg)	Intraocular pressure in mmHg, measured utilizing a Goldmann tonometer	Screening, Days 28, 84

1.6.6 Other Assessment

Subjects will rate the comfort of IP instillation at Days 1, 7, 14, 28, 56, 84 according to the following 4-point scale:

0 = No discomfort
1 = Mild discomfort
2 = Moderate discomfort
3 = Severe discomfort

1.6.7 Subject Withdrawal Criteria

The following are the criteria for considering withdrawal from the study:

- Withdrawal of subject consent. The subject may request for any reason at any time to be withdrawn from the study.
- The Sponsor terminates the study.

If a subject withdraws from the study, the reason for withdrawal will be recorded in the eCRF.

If a study subject fails to attend a study visit at any point during the study period, every effort should be made to keep the subject in the study and conduct all study visits as scheduled; all attempts to contact the subject must be documented.

1.7 Study Data

The study data to be analyzed include all clinical data captured by eCRF. The eCRF database will be locked for the final analyses.

2 GENERAL ANALYSIS DEFINITIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.4 or higher. No imputation will be performed for missing data unless stated otherwise. Listings for CSR Appendix 16.2 will include, as a minimum, all the subject data points to be used for analyses. Data listings will be provided for all subjects with data available.

2.1 Study Eye

Based on the protocol, for subjects with a qualifying SANDE score who meet all other inclusion/exclusion criteria, the eye with the lower TBUT at Visit 2/Day 1 will be designated as the study eye. In the event both eyes have the same TBUT scores, the eye with the lower Schirmer's test score will be designated as the study eye. If both eyes have the same TBUT and Schirmer's test scores, the right eye will be designated as the study eye.

The study eyes for analyses were based on the study eyes designated by eCRF according to above criteria.

2.2 Treatment Groups

All the analyses will be conducted by four individual treatment groups that will be labelled as 0.1% SDP-4, 1.0% SDP-4, 3.0% SDP-4, and Vehicle. The subjects receiving SDP-4 may be pooled for data summary as appropriate, and will be labeled as "All SDP-4".

2.3 Treatment Period, Visit, and Day

The overall study consists of initial Screening, Run-In, and one Treatment Period.

A reference date refers to the date of the first randomized IP administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date. The relative day will be defined as: visit date – reference date + 1 for visits on or after the reference date, and visit date – reference date for visits before the

reference date.

2.4 Definition of Baseline

In general, the baseline is defined as the last assessment before the intake of the first randomized IP unless specifically stated otherwise. Pre-dose unscheduled assessments will be taken into account for baseline determination.

2.5 Out of Window and Unscheduled Visits

All scheduled assessments after first administration of randomized IP will be used. The protocol defined windows for scheduled visits will not be used in the analyses by visit. Data will be assigned to the scheduled visit closer in time to the scheduled visit. Unscheduled visit data will only be used in an analysis if there is no other available data closer in time to a scheduled visit. Post first dose unscheduled assessments will be taken into account for worst-case determination as applicable. All unscheduled visit data will be included in data listings.

2.6 Analysis Populations

2.6.1 Screened Population

All subjects who were screened and signed the informed consent are included in the Screened Population (SCRN).

2.6.2 Intent-to-Treat (ITT) Population

The ITT population will include all randomized subjects who received IP. This population will be the primary population for efficacy analyses and will be used to summarize all efficacy variables by the treatment group as randomized.

2.6.3 Per Protocol (PP) Population

The PP population is a subset of the ITT population, which will include all subjects who complete the study without major protocol deviations. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables by the treatment group as treated.

2.6.4 Safety Population

All safety endpoints will be evaluated on the Safety Population (SAF), consisting of all randomized subjects who received at least one dose of randomized IP and will be analyzed by the treatment group as treated.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations prior to final database lock.

A summary table of number (%) of patients in each analysis population/set will be provided.

2.7 Unit of Analysis

In general, the unit of analysis will be study eye and non-study eye for eye-level measurements, and subject for subject-level measurements.

2.8 Definition of Subgroups

No subgroup analyses are planned.

2.9 Descriptive Summaries

Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used. All tabulated summaries will include all 4 individual treatment groups and the All SDP-4 group (combined from the 3 SDP-4 dosing groups) as described in Section 2.2. For endpoints that are continuous in nature: number of observations, mean, median, minimum and maximum, and standard deviation (SD) values will be presented as descriptive statistics summary for both observed values and change from baseline values at each scheduled visit if applicable. For endpoints that are categorical in nature: frequency counts and percentages will be presented as descriptive statistics summary at each scheduled visit if applicable.

The number of decimal places to display for calculated data will be determined by the original scale of the data. Means and medians will be reported with one (1) additional decimal place. Standard deviation will be reported with two (2) additional decimal places. Minimum and maximum will be reported with the same number of significant digits as the method of capture.

3 SUBJECT INFORMATION

In general, all subject information will be summarized for the ITT Population based on randomized treatment group, unless stated otherwise.

3.1 Disposition Information

Summaries will be provided for number and percentage of completed or discontinued study with the reasons of discontinuation as collected on eCRF.

3.2 Study Visits

The number and percentage of subjects completing each scheduled visit will be tabulated.

3.3 Demographics and Baseline Characteristics

Descriptive statistics or frequency tabulation will be provided for age, gender, race, ethnicity, and iris color.

3.4 Medical and Ocular History

A summary table will be prepared for the medical history data, and one for ocular history data. Conditions will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA). This table will indicate the number and percentage of subjects who presented with previous history overall and by system organ class and preferred term.

3.5 Pregnancy Status

The data for urine pregnancy testing will be presented in a listing, for female subjects with childbearing potential only.

3.6 Protocol Deviations

All reported major protocol deviations and determined exclusions from any analysis population(s) will be documented and included in the CSR. The number and percentage of subjects who met any inclusion or exclusion exceptions will be summarized by excepted inclusion and exclusion criteria.

4 TREATMENTS AND MEDICATIONS

In general, all treatment parameters will be summarized for the Safety Population based on actual treatment group, unless stated otherwise. All reported medications will be coded using World Health Organization-Drug Dictionary (WHO-DD).

4.1 Prior Medications

Summary tables will be prepared for the reported use of all non-study drugs by generic name (including prescribed and over the counter medications) that were taken prior to enrollment but that were discontinued prior to receiving the first administration of the randomized study treatment at Visit 2.

4.2 Concomitant Medications

Summary tables will be prepared for the reported use of all non-study drugs by generic name (including prescribed and over the counter medications) that were taken subsequent to receiving the first administration of the randomized study treatment at Visit 2, regardless of when use started.

4.3 Extent of Exposure

4.3.1 Extent of Exposure to Run-in Study Medication

Extent of exposure to run-in study medication will be calculated as days on vehicle, defined as one plus the difference in days between the date of last instillation as recorded at Day 1 and the visit date at which medication was first dispensed (Screening).

Overall, extent of exposure to run-in study medication will be summarized using descriptive statistics. Extent of exposure to run-in study medication will also be presented (N and %) by the following intervals: 1 to 7 days, and >7 days.

4.3.2 Extent of Exposure to Randomized Study Medication

Extent of exposure to randomized study medication is calculated as days on therapy, defined as one plus the difference in days between the date of last instillation and the date at which randomized medication was first dispensed. For subjects for whom the date of last dose is unknown, extent of exposure will be calculated based on the date of last contact.

Overall, extent of exposure to randomized study medication will be summarized using descriptive statistics. Extent of exposure to randomized study medication will also be presented (N and %) by the following intervals: < 8 days, 8 to 28 days, 29 to 56 days, 57 to 84 days, and > 84 days.

4.4 Artificial Tears

The amount of used and unused artificial tears will be documented by site personnel starting at Visit 2 through Visit 7 if the artificial tears were required by the subject. The number and percentage of subjects who used artificial tears at

least once during the study will be tabulated. Among subjects who used artificial tears at least once during the study, the overall amount of used artificial tears will be summarized using descriptive statistics.

5 EFFICACY

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint
Mean change from baseline in total SANDE score at Visit 7/Day 84

5.1.2 Secondary Efficacy Endpoints

- Mean and mean change from baseline at each visit for each of the following evaluations:
  - Conjunctival lissamine green staining (combined and each zone)
  - Corneal fluorescein staining (combined and each zone)
  - TBUT
  - Anesthetized Schirmer's test at Visit 7/Day 84
  - Conjunctival hyperemia
  - Individual symptom VAS scores, separately for each symptom
- SANDE
  - Mean and mean change from baseline in total SANDE score at each visit, excluding Visit 7/Day 84
  - Mean and mean change from baseline in SANDE severity score at each visit
  - Mean and mean change from baseline in SANDE frequency score at each visit

5.2 Type 1 Error Control for Multiple Tests

In order to minimize the impact of multiplicity in this dose-response study, a gatekeeping procedure will be followed to conduct the following analyses in a hierarchical order:

1. Primary (SANDE) high concentration vs. vehicle
2. Primary (SANDE) middle concentration vs. vehicle
3. Primary (SANDE) low concentration vs. vehicle

The comparisons will be conducted at $\alpha = 0.05$. Each comparison will be made in order until $p >$ (exceeds) 0.05. If $p \leq 0.05$, the comparison is statistically significant and testing is continued.

5.3 Handling of Missing Data

For efficacy analyses, use of a mixed model for repeated measures (MMRM) approach requires only that data are missing at random so that no other method will be employed to deal with missing data. It may be necessary to test whether this assumption applies to the data set. For sensitivity analysis the last observation carried forward (LOCF) will be used for missing data imputation.

5.4 Methods of Efficacy Analysis

Each endpoint will be summarized for each visit where that endpoint is assessed. Where appropriate, the change from baseline value will be used to assess the difference between each concentration of SDP-4 and vehicle.

Change from baseline endpoints will be analyzed using MMRM analysis with terms for baseline measurement, treatment, visit, and treatment-by-visit interaction. An unstructured variance-covariance matrix will be employed to account for within subject correlation in the repeated measures. In case of model non-convergence a simpler variance-covariance matrix will be employed. Within treatment estimate of least square mean change from baseline and associated standard error will be provided by visit. Also, estimate of difference in least square means of change from baseline between each SDP-4 group and Vehicle (i.e. the estimand) and associated standard error and 95% confidence interval will be provided by visit.

The MMRM analysis is based on a standard linear mixed model, defined as:

$$Y = \mu + B_i + T_t + V_j + TV_{tj} + \underline{\varepsilon_{itj}}$$

Where Y denotes an outcome variable, μ is the overall mean, B_i is the baseline value, T_t is the fixed effect due to t^{th} treatment group, V_j is the fixed effect due to the j^{th} visit, TV_{tj} is the treatment by visit interaction, and $\underline{\varepsilon_{itj}}$ is the measurement error associated with the individual subject.

Following is a sample SAS code for MMRM analysis:

```
proc sort data=datain; by subject_id visit;
ods select diffs lsmeans;
proc mixed data=datain method=reml;
  class subject_id treat visit;
  model cfb_var= baseline treat visit visit*treat / solution rcorr;
  repeated visit / type=un subject=subject_id rcorr;
  lsmeans visit*treat / pdiff;
run; quit;
```

For variables with only one post-baseline assessments (e.g. Schirmer's test), change from baseline will be analyzed utilizing analysis of covariance (ANCOVA) with terms for baseline measurement and treatment. The mathematical form of the ANCOVA model is also based on a standard linear mixed model, defined as:

$$Y = \mu + B_i + T_t + \underline{\varepsilon_{it}}$$

Where Y denotes an outcome variable, μ is the overall mean, B_i is the baseline value, T_t is the fixed effect due to t^{th} treatment group, and $\underline{\varepsilon_{it}}$ is the measurement error associated with the individual subject.

Following is a sample SAS code for ANCOVA analysis:

```
proc sort data=datain; by subject_id;
ods select diffs lsmeans;
proc mixed data=datain method=reml;
  class treat;
```

```
  model cfb_var= baseline treat / solution rcorr;
  lsmeans treat / pdiff;
run; quit;
```

5.5 Approaches to Efficacy Analyses

The following table describes detailed approaches to analyze each specific efficacy endpoint.

Table 4. Summary of efficacy analyses

Endpoint	Type	Statistical Method	Population (Eye)	Missing Data Handling
Mean change from baseline in total SANDE score at Visit 7/Day 84 (including all post-baseline visits in the analysis)	Primary	MMRM	ITT	MMRM
	Supportive	MMRM	PP	MMRM
	Sensitivity	MMRM	ITT	LOCF
Mean change from baseline at each visit for TBUT (including all post-baseline visits in the analysis)	Secondary	MMRM	ITT (SE&NE)	MMRM
Mean change from baseline at each visit for conjunctival lissamine green staining (combined and each zone)	Secondary	MMRM	ITT (SE&NE)	MMRM
Mean change from baseline at each visit for corneal fluorescein staining (combined and each zone)	Secondary	MMRM	ITT (SE&NE)	MMRM
Mean change from baseline at Day 84 for Schirmer's test	Secondary	ANCOVA	ITT (SE&NE)	No imputation
Mean change from baseline at each visit for conjunctival hyperemia	Secondary	MMRM	ITT (SE&NE)	MMRM

Mean change from baseline at each visit for Individual symptom VAS scores, separately for each symptom	Secondary	MMRM	ITT	MMRM
Mean change from baseline in SANDE severity score at each visit	Secondary	MMRM	ITT	MMRM
Mean change from baseline in SANDE frequency score at each visit	Secondary	MMRM	ITT	MMRM

Note: SE = Study Eye, NE = Non-Study Eye

6 SAFETY

All safety parameters will be summarized based on the actual treatment group based on the Safety Population. Subject is the unit of analysis for all safety variables. Subject-level data will be generated for eye-specific safety variables as described below.

6.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are those with onset after randomization or if occurring prior to randomization, worsened after randomization. Only treatment-emergent events will be summarized. All events in the clinical database regardless of when they occurred will be provided in data listings. Adverse events will be classified according to the MedDRA to the levels of System Organ Class (SOC) and primary Preferred Term (PT).

Run-in AEs that occurred during the run-in period on vehicle (Note: subjects may be on run-in vehicle for up to 16 days, but no less than 12 days) will be summarized separately.

An overall summary will be presented which gives the number and percentage of subjects that experienced any TEAE, experienced any treatment related TEAE, permanently discontinued treatment due to a TEAE, interrupted treatment due to a TEAE, experienced a treatment emergent SAE, and that died.

The number and percentage of subjects experiencing one or more events will be tabulated separately for ocular AEs and non-ocular AEs by SOC and PT. In addition similar tables by SOC and PT will be displayed further by maximum severity, and by closest relationship to treatment.

In summary tables for ocular adverse events, AEs occurring in both eyes will be summarized once at the greater severity or closer relationship to study drug.

The number of and percentage of subjects experiencing AEs leading to premature discontinuation from the study will be tabulated and listed.

A listing of serious TEAEs will be also provided.

A glossary listing that shows the verbatim terms assigned to each SOC and PT will be provided.

6.2 Visual Acuity

Descriptive statistics of the observed and change from baseline BCVA expressed as equivalent logMAR will be tabulated for each eye (study eye and non-study eye) by visit. In addition, the number and percentage of subjects with a ≥ 3-line decrease from baseline in BCVA will be tabulated for each eye (study eye and non-study eye) by visit and at any visit.

6.3 Intraocular Pressure

Descriptive statistics of the observed and change from baseline IOP will be tabulated for each eye (study eye and non-study eye) by visit. In addition, the number and percentage of subjects with ≥ 10 mmHg increase from baseline in IOP will be tabulated for each eye (study eye and non-study eye) by visit and at any visit.

6.4 Slit-Lamp Examination

Observed results will be summarized for each anterior ocular structure (Lid, Conjunctiva, Cornea, Anterior chamber, Iris/Pupil, Lens status) in frequency tables for each eye (study eye and non-study eye) by visit.

6.5 Dilated Fundus Examination

Observed results will be summarized for each structure (i.e. vitreous, optic nerve, macula, peripheral retina, cup-to disc ratio) in frequency tables for each eye (study eye and non-study eye) by visit.

7 OTHER ASSESSMENT

IP comfort assessment results will be summarized in a frequency table by visit.

8 CHANGES FROM PROTOCOL

- Following analyses have been removed from hierarchy of analyses as described in protocol Section 9.5.3 Efficacy analysis:
  - Secondary (TBUT) high concentration vs. vehicle
  - Secondary (TBUT) middle concentration vs. vehicle
  - Secondary (TBUT) low concentration vs. vehicle
- IP comfort assessment has been disregarded as one of the safety assessments.

- **REFERENCES**

None

9 TABLES, LISTING, FIGURES

9.1 List of Tables

Table Number	Table Title	Study Population
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9.2 List of Listings

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16.2.5.3	Treatment Exposure	SAF
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None