STATISTICAL ANALYSIS PLAN

A Randomized, Double-Masked, Vehicle-Controlled Crossover Clinical Trial to Assess Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease

Sponsor: Aldeyra Therapeutics, Inc.

Protocol Number: ADX-102-DED-027

[redacted]

[redacted]

Date: 14-Jun-2022

Version: 1.0

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Statistical Analysis Plan Approval

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List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CFB	Change From Baseline
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
DEC	Dry Eye Chamber
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
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
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAAS	Software-as-a-Service
SAE	Serious Adverse Event
SANDE	Symptom Assessment in Dry Eye
SAP	Statistical Analysis Plan
SD	Standard Deviation
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
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the statistical analyses to be applied to data resulting from study protocol ADX-102-DED-027, version 1.0 dated 04Feb2022. Although the primary objective of the SAP is to detail the statistical procedures that will be used, various other details have been selectively included. These details convey aspects of the experimental design and study procedure considered to be important to a fully informed understanding of the context underlying the analyses, and therefore the aim and purpose of the analyses.

This SAP has been 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).

[redacted]

Additional analyses other than the planned analyses described herein may be conducted as ad-hoc analyses. All ad-hoc analyses will be identified in the CSR. The intent of any such analyses would be to better characterize treatment effects.

2. Summary of Statistical Deviations from the Protocol

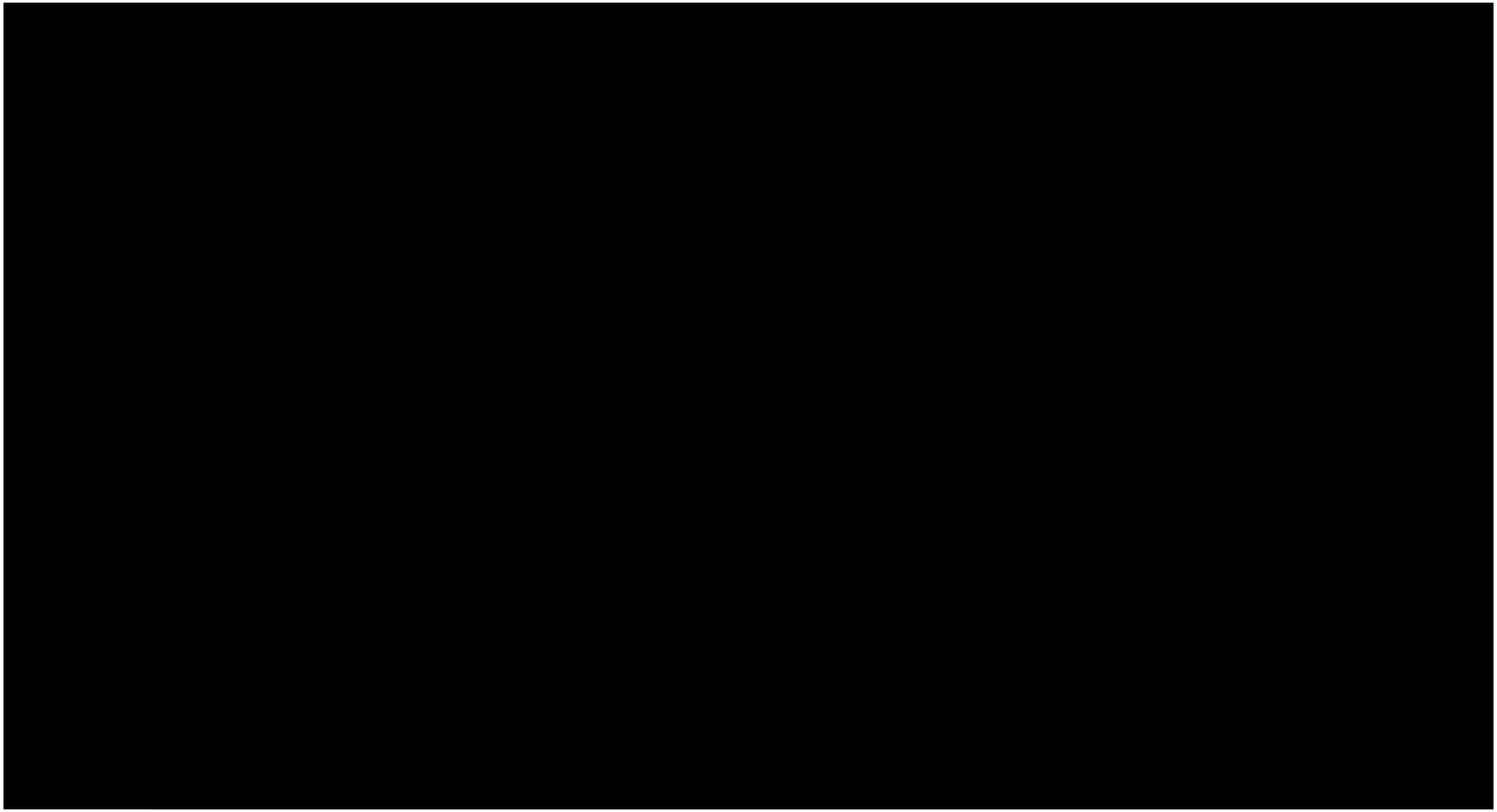
Analyses outlined in this SAP are in all instances thought to be compatible with or complimentary to the more general presentation found in the protocol.

3. Study Objectives

The general study objective is to evaluate the efficacy of reproxalap in subjects with dry eye disease, as assessed by conjunctival redness, Schirmers test, and ocular symptoms. [redacted]

4. Study Variables

Efficacy variables and safety variables follow. Prior to a listing of each variable, the Study Schematic from the protocol has been inserted. This schematic summarizes the variables that will be collected and conveys important features of the experimental design that further inform the collection of variables.



4.1 Efficacy Variables

The efficacy variables include the following:

4.1.1 PRIMARY ENDPOINTS:

- Change from baseline in Schirmers test prior to and after the final of four doses at visit 2 and visit 4.
- Change from baseline in conjunctival redness on a 9-point scale (0-4) over 90 minutes in the DEC at visit 3 and visit 5.

4.1.2 SECONDARY ENDPOINTS:

- Responder event rate where “response” is defined as a Schirmers test of ≥10mm that is assessed before and after the final dose at both visit 2 and visit 4.
- Conjunctival Redness measured at designated times outside the DEC
- VAS for ocular dryness, discomfort, burning, grittiness, and stinging measured at designated times for all visits

4.2 Safety Variables

The safety variables include the following:

- Snellen visual acuity (SVA)
- Slit-lamp examination (SLE)
- Intraocular pressure (IOP)
- Adverse event (AE) query
- Concomitant Medications
- Intraocular Pressure (IOP)

5. Study Design and Procedures

5.1 General Study Design

This is a Phase 2b, randomized, double-masked, vehicle-controlled, crossover clinical trial to assess efficacy and safety of 0.25% reproxalap ophthalmic solution compared to vehicle in subjects with dry eye disease. Assessments are carried out both within and without DEC presence. The clinical trial will consist of 6 visits to the clinic over a period of approximately 19 to 39 days. [redacted]

[redacted]

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	[redacted]	[redacted]
Visit 1a	Day -21	[redacted]	[redacted]
Visit 1b	Day -14	[redacted]	[redacted]
Visit 2	Day 1	[redacted]	[redacted]
Visit 3	Day 2	[redacted]	[redacted]
		[redacted]	[redacted]
Visit 4	Day 10	[redacted]	[redacted]
Visit 5	Day 11	[redacted]	[redacted]
		[redacted]	[redacted]

5.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided along with other features of the experimental design in the Protocol Study Schematic located on pages 7 and 8 of this document.

5.3 Inclusion – Exclusion Criteria and General Study Population

The inclusion and exclusion criteria are enumerated and described in the protocol and have not been repeated in this SAP. The inclusion and exclusion criteria apply to all subjects.

6. Study Treatments

6.1 Method of Assigning Subjects to Treatment Condition

Before the initiation of study at Screening Visit 1a, each subject who provides written and informed consent will be assigned to a screening number. All screening numbers will be assingned in strict numerical sequence at a site and no numbers will be skipped or omitted. Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1a/b and Visit 2 will be assigned a randomization number at the end of Visit 2. The Interactive Web Response System (IWRS) will be used to assign all randomization numbers.

Randomization and kit numbers will be assigned automatically to each subject as they are entered into the IWRS.

The sequence in which subjects receive investigational product (reproxalap or vehicle) will be determined by randomization. [redacted] Randomization of subjects to one of the treatment sequences will be based on the randomization scheme.

Subjects will be randomized to one of two sequences: AB or BA.

Sequence	Treatment Period 1	Treatment Period 2
AB	Reproxalap	Vehicle
BA	Vehicle	Reproxalap

The randomization schedule will use block randomization, such that there will be an approximately equal number of subjects assigned to each of the two treatment sequences. Both the randomization number and the dispensed study drug kit number(s) will be recorded on the subject's source document and eCRF. The Sponsor, investigators, and study staff will be masked during the randomization process and throughout the study.

6.2 Masking and Unmasking

In general, the final, open statistical analysis will be performed without the possibility of data alteration. Procedures to insure this are described in some detail in what follows.

The Sponsor, investigators, qualified site personnel (except delegated unmasked pharmacy staff), and subjects will be masked to the investigational product administered [redacted]

[redacted]

Emergency unmasking should only be performed when necessary to treat the subject. Most often, knowledge of the possible treatment assignments is sufficient to treat a clinical trial subject who presents with an emergency condition.

The investigator shall make every effort to contact the Medical Monitor to discuss the subject's emergency and the need to unmask prior to unmasking any subject.

In situations in which the investigator has tried but is unable to reach the Medical Monitor, best judgment on the part of the investigator should be used, based on the nature and urgency of the clinical situation. Pending appropriate conditions, the investigator may proceed with unmasking without having successfully reached and discussed the situation with the Medical Monitor. Once a subject's treatment assignment has been unmasked, the Medical Monitor should be notified within 24 hours of the unmasking of the treatment, without revealing the treatment.

If the investigator determines that emergency unmasking is necessary, the investigator should identify the given subject's IP kit, which contains a scratch-off laminate under which the treatment is identified, along with the associated lot number. In order to unmask, the investigator should scratch off the laminate, using a flat object and applying pressure, to reveal the treatment assigned for that subject.

The emergency unmasking should be performed by the designated site personnel. The investigator must also indicate in source documents and the Case Report Form (CRF) that the mask was broken and provide the date, time, and reason for breaking the mask.

Any AE or Serious Adverse Event (SAE) associated with breaking the mask must be recorded and reported as specified in the protocol. The investigator has the responsibility to contact the Sponsor in the event of a drug-related, serious, unexpected AE. [redacted] will be provided with the treatment assignment for the subject for regulatory reporting.

If treatment assignment is unmasked, the treatment will be discontinued immediately, and the subject will be discontinued from the clinical trial.

The mask may be broken in the case of pregnancy should the subject desire this information.

7. Sample Size and Power Considerations

Approximately 160 subjects with dry eye disease will be screened in order to randomize and realize study completion in approximately 50 subjects. Approximately 25 subjects will be assigned to one of two (2) treatment sequences, namely, AB (reproxalap then vehicle) or BA (vehicle then reproxalap).

[redacted]

[redacted]

In order to account for dropout and to assess safety and the other secondary endpoints, a total of 50 subjects will be randomized. [redacted]

8. Data Preparation

A study chart/record will be maintained on-site for each subject to file records such as general observations, medical and medication use history, physical examination, clinical laboratory data source documents, and related documentation. The original record will be considered the data 'source document'. The source documents will be available for inspection (direct/remote) by the study monitors and/or representatives before, during, or upon completion of the study. Good documentation practices will be followed for source documentation. All corrections will be dated and initialed. The Investigator will retain the originals.

All clinical study data not available via electronic source will be collected by the Investigator and staff and recorded on source documents. The Investigator will assume responsibility for ensuring the completeness and accuracy of all clinical documents.

This clinical trial will be conducted, and the data will be generated, documented (recorded), and reported in compliance with the protocol, GCP standards, ICH, and other applicable local laws and regulations.

[redacted] staff will be appropriately trained to ensure the collection of accurate, consistent, complete, and reliable data are entered onto an electronic case report form (eCRF) unique for each subject.

All data collected in the study will be captured and maintained in a secure and validated electronic data capture (EDC) system. [redacted] staff will enter the data for each subject into an eCRF, with the exception of the data collected in an electronic or paper source (e.g., lab data, diary data, etc.). Data source will be described in the Data Management Plan (DMP).

The eCRF and/or diaries will contain edit checks and/or controls to ensure the quality, integrity, accuracy, and completeness of the data entered. The Medical Monitor (medical representative) may examine eCRF and diary data for preliminary medical review (direct/remote).

The eCRF data will be maintained in a validated study database with an audit trail of all changes that are made to the database, including the reason for the data change. AEs will be coded using a standard dictionary, Medical Dictionary for Regulatory Activities [redacted] while concomitant medications will be categorized using the World Health Organization Drug Dictionary [redacted] at the start of the study.

Creation and validation of the EDC system and management of the data will be conducted. Methods used to ensure the quality and integrity of the data will be documented in the DMP, which will be approved by the Data Management provider and the Sponsor.

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

- All data management requirements are met according to 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 [redacted] and Aldeyra Therapeutics, Inc. personnel;
- Protocol deviations have been identified and status defined (major/minor deviations);
- Analysis populations have been determined; and
- Randomized treatment codes have been unmasked.

9. Management of Analysis Data

9.1 Covariates and Subgroups

9.1.1 PLANNED COVARIATES

[redacted]

9.1.2 SUBGROUPS

None are planned.

9.2 Interim Analyses

No interim analyses are planned.

9.3 Handling of Early Termination Visit Information

[redacted]

9.4 Pooling of Study Centers

[redacted]

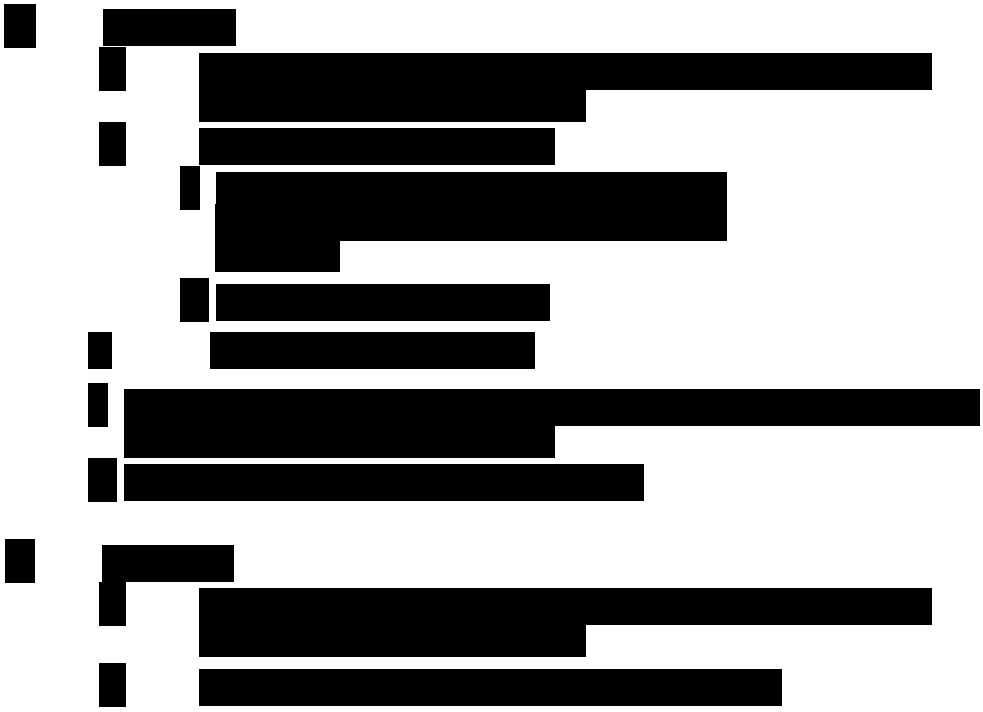
9.5 Missing Data

[redacted]

9.5.1 HANDLING OF MISSING DATE VALUES

9.5.1.1 Partial or Missing Dates

[redacted]



[redacted]

10. 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 on the safety population. The analysis of efficacy data will be performed on the ITT population and on the PP population to provide sensitivity analyses.

10.1 Intent-to-Treat

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

10.2 Per Protocol

The PP population includes subjects in the ITT population subject who received at least one dose of IP who met all inclusion/exclusion criteria, and who did not incur a major protocol deviation. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.

10.3 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.

11. General Statistical Considerations

11.1 Unit of Analysis

[redacted]

11.2 Missing or Inconclusive Data Handling

Minimal data loss is anticipated and a need for imputation applied to missing values and/or other procedures (e.g., tipping point analysis) is not expected. [redacted]

11.3 Definition of Change Score

[redacted]

12. 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. [redacted] This information will be presented for the ITT, PP, and Safety populations. In general, percentages will be calculated using randomized subjects as the denominator (with any exceptions noted).

[redacted]The reasons for study discontinuation that will be summarized include AE, protocol deviation, 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 major protocol deviations will be summarized by sequence, period, treatment ignoring sequence, and all subjects, for all randomized subjects. The protocol deviations that will be summarized include: 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.

[redacted].

13. Demographic, Body Habitus and Pretreatment Variables

13.1 Demographic and Body Habitus Variables

The demographic and body habitus variables collected in this study include age, sex, race, ethnicity, height, and weight. [redacted]

Age (years) will be summarized using continuous descriptive statistics. Further, age will 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, and ethnicity by eye (OD and OS, separately).

A subject listing that includes all demographic variables for the ITT population will be provided.

13.2 Pretreatment Variables

Baseline disease characteristics captured by the Schirmers test, IOP, and VA will be summarized for all subjects by eye. [redacted]

14. Medical History and Concomitant Medications

14.1 Medical History

[redacted]

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment condition at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. Ocular medical history will be similarly summarized at the subject 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.

14.2 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary [redacted] and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active

ingredient is not provided or includes more than two ingredients (e.g., multivitamins) then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

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 by treatment-period. Ocular and non-ocular medications will be summarized separately. Medications will be tabulated for each treatment condition 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 condition. Listings of concomitant medications will be generated separately for ocular and non-ocular data.

15. Dosing Compliance and Treatment Exposure

15.1 Dosing Compliance

An Investigator will be on-site for dosing and on-call throughout the two-day duration of the study; thus, significant percentages of major deviations as a result of dosing compliance are not expected.

15.2 Treatment Exposure

Extent of treatment exposure for subjects will be calculated in days using the following:

Extent of Exposure (days) = Date of completion/discontinuation – 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

The presentation of extent of treatment exposure will use the safety population. A subject listing of treatment exposure will also be produced that will include overall exposure. [redacted]

16. Efficacy Analyses

16.1 Analysis of the Primary Efficacy Endpoint(s)

There are two primary efficacy endpoints: 1) the Schirmers test score; and 2) the conjunctival redness score. The primary endpoints will be assessed using mixed model repeated measures (MMRM). [redacted]

[redacted]

For any model, effects other than treatment and baseline with p values of 0.1 or greater may be removed optionally without consideration of convergence.

[redacted]

16.2 Analysis of the Secondary Endpoints and Secondary Analyses of Primary Endpoints

The secondary endpoints are the following:

- Schirmer test responder event rate (≥ 10mm) measured before and after the final dose at visit 2 and 4.
- Conjunctival Redness measured outside the DEC for visit 2 and visit 4 at pre-dose and 10 minutes after doses 1, 2, and 3; and
- VAS for ocular dryness, discomfort, burning, grittiness and stinging, and ocular itching, [redacted]

Statistical models and procedures that are analogous to those used for the primary efficacy analyses will be employed to evaluate secondary endpoints. [redacted]

Secondary analyses of the primary endpoints will be repeated using the PP population.

16.3 Multiplicity Considerations

P-values for the main effect of treatment will be ordered for the primary endpoints and Hochberg's procedure for multiplicity control will be used. [redacted]

No type I error control will be utilized for exploratory endpoints. Thus, exploratory comparisons are considered hypothesis generating.

17. Safety Analysis

All safety analyses will be conducted using the safety population.

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. [redacted]

[redacted]

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 display the number of subjects who experience one or more AEs in each of the following categories:

- All TEAEs regardless of severity or presumed relationship to Study Intervention
- Treatment-Emergent AEs judged related to Study Intervention
- Treatment-Emergent Severe Adverse Events
- Treatment-Emergent Severe Adverse Events judged related to Study Intervention
- Treatment-Emergent Serious Adverse Events
- Treatment-Emergent Serious Adverse Events judged related to Study Intervention
- Treatment-Emergent Adverse Events with Fatal Outcome
- Treatment-Emergent Adverse Events with Fatal Outcome judged related to Study Intervention
- Treatment-Emergent Adverse Events leading to Withdrawal from the Study
- Treatment-Emergent Adverse Events leading to Withdrawal from the Study judged related to Study Intervention

The number of emergent events and the number and percentage of subjects with TEAEs will be summarized by treatment-period. SOC and PT for different categories of TEAEs. At each level of tabulation (e.g., at the PT level) subjects will be counted only once if they had more than one such event reported during the AE collection period.

The following summary tables will be presented for TEAE data:

- Treatment-Emergent Adverse Events Overview
- Treatment-Emergent Adverse Events, by Severity and Grade
- Treatment-Emergent Adverse Events, by SOC and PT
- Treatment-Emergent Severe Adverse Events, by SOC and PT
- Treatment-Emergent Serious Adverse Events, by SOC and PT
- Treatment-Emergent Adverse Events with Fatal Outcome, by SOC and PT

- Treatment-Emergent Adverse Events leading to Withdrawal from the Study, by SOC and PT
- Treatment-Emergent Drug Related Adverse Events, by SOC and PT
- Treatment-Emergent Severe Drug Related Adverse Events, by SOC and PT
- Treatment-Emergent Serious Drug Related Adverse Events, by SOC and PT
- Treatment-Emergent Drug Related Adverse Events with Fatal Outcome, by SOC and PT
- Treatment-Emergent Drug Related Adverse Events leading to Withdrawal from the Study, by SOC and PT

'Severe' will be defined as Grade 3 or above. A missing severity will be considered Grade 3.

'Drug Related' will be defined as 'Definitely Related', 'Probably related' or 'Possibly Related', excluding 'Unlikely Related' and 'Not Related'. A missing relationship will be considered as 'Definitely Related'.

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

- Ocular TEAEs
- Non-ocular TEAEs

17.1 Deaths, Serious Adverse Events and Other Significant Adverse Events

17.1.1 Deaths

All deaths occurring up to the analysis cut-off date, regardless of causality, will be summarized by cause of death.

17.1.2 Serious Adverse Events

A listing of Serious Adverse Events (SAEs) occurring up to the analysis cut-off date will be provided.

SAEs occurring before study drug initiation will be listed separately.

17.1.3 Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study

A listing of all AEs occurring up to the analysis cut-off date and leading to discontinuation of study drug or withdrawal from study will be presented.

18. Other Safety Variables

18.1 Visual Acuity (ETDRS)

The Snellen Visual Acuity (SVA) will be performed pre-DEC (and pre symptom assessment) and again at post-DEC exposure. 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. 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 OD and OS, separately. Continuous descriptive statistics by visit for each treatment condition will be presented. A subject listing of VA will also be produced.

18.2 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, and lid will be performed pre-DEC (and pre symptom assessment) and again at post-DEC exposure. 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 condition at each visit for OD and OS, separately. Percentages will be based on the number of subjects in each treatment condition with responses. Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing each follow-up visit to baseline (Visit 1b). A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

18.3 Intraocular Pressure (IOP)

IOP will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg. Intraocular Pressure (IOP) will be performed prior to DEC entry. 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 OD and OS, separately, will be summarized using continuous descriptive statistics by visit and eye for each treatment condition and for all actively treated subjects. A subject listing of IOP also will be produced.

19. Additional Analyses

Additional analyses other than the planned analyses described herein may be conducted as ad-hoc analyses. All ad-hoc analyses will be identified in the CSR. The intent of any such analyses would be to better characterize treatment effects.

20. Revision History

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

21. Reporting Conventions

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

21.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a CSR.
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be presented in color with treatment condition distinguished by different symbols and colors. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g.,μ,α,β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, figures, and data listings.
- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are

planned, then a cover page may be used to display footnotes.

- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2013-05-17) ISO 8601 format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study, also in ISO 8601 format.
- Time durations will be reported in mixed HHh MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g., 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures, and data listings will have the Table, Listing, or Figure status (DRAFT, FINAL), and a date/time stamp on the bottom of each output.
- All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

21.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as “Population: <name of population>” and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., FAS Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.
- Population sizes are presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes with non-missing values or subset shown with summary statistics are represented with (n) of subjects.

- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include: N, mean, SD, minimum, and maximum. Other summaries (e.g., number missing, median, quartiles, 5%, 95% Confidence Intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to xx.x%. A percentage of 100% will be reported as 100%. No value of 0% will be reported. Any computation of percent that results in 0% is to be presented as a blank.
- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (0.0001). All p-values reported on default output from statistical software (i.e., SAS® Software version) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not 0.0000.

22. References

N/A