# STATISTICAL ANALYSIS PLAN

**A Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled Phase 3 Clinical Trial to Assess the 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-032

Author: [redacted]

Date: 20-Jun-2024

Version: 1.0 Final

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**Statistical Analysis Plan Approval**

## Table of Contents

List of Abbreviations

| | |
|---|---|
| ATC | Anatomical Therapeutic Chemical Classification |
| [redacted] | [redacted] |
| CS | Clinically Significant |
| CSR | Clinical Study Report |
| eCRF | Electronic Case Report Form |
| ETDRS | Early Treatment of Diabetic Retinopathy Study |
| HIPAA | Health Information Portability and Accountability Act |
| ICH | International Conference on Harmonization |
| ITT | Intent-to-Treat |
| logMAR | Logarithm of the Minimum Angle of Resolution |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed-model repeated measures |
| NCS | Not Clinically Significant |
| PP | Per Protocol |
| PT | Preferred Term |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| VAS | Visual Analog Scale |

## 1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the statistical analyses to be applied to data resulting from trial protocol ADX-102-DED-032: A Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease.

Although the primary objective of the SAP is to describe the statistical procedures that will be used, various other details have been selectively included. These details convey aspects of the experimental design and trial procedures 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 (CSRs).

This SAP describes the data that will be analyzed to reveal subject characteristics, trial efficacy, and trial safety. Whereas the protocol presents a general discussion of statistical procedures, this SAP provides greater detail and further clarifies a particular application of a general procedure. Nevertheless, *in the event* of any discrepant directives between the protocol and the SAP, the SAP will supersede the protocol.

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.

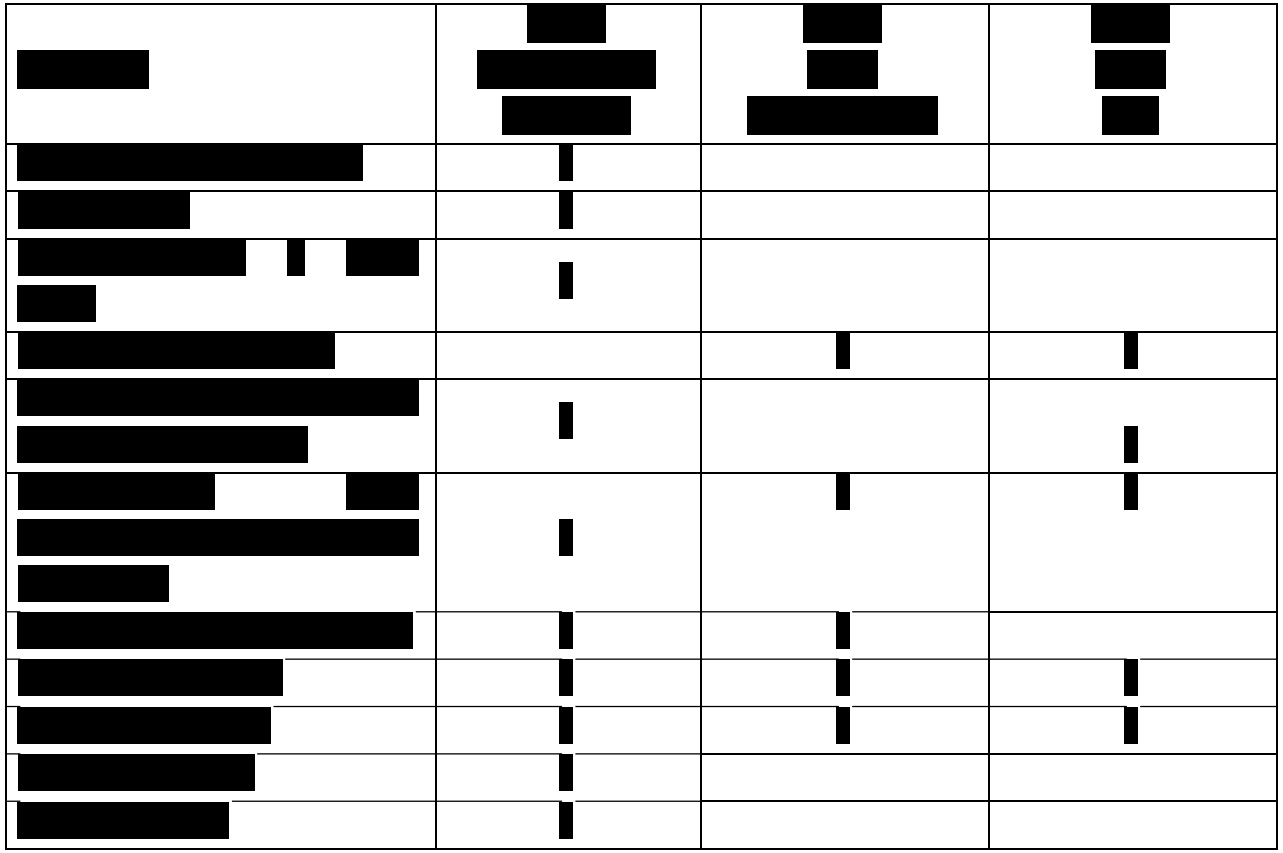
## 3. Trial Objectives

The general trial objective is to evaluate the efficacy of reproxalap in subjects with dry eye disease, as assessed by the primary endpoint of subject-reported ocular discomfort. As appropriate, these measurements occur prior to and after dosing, and within and outside a [redacted] (CAE).

## 4. Trial Variables

Efficacy and safety variables will be considered in what follows. The Schedule of Visits and Measurements that immediately follows summarizes the trial variables and conveys the trial's experimental design, including data collection time points. Together, the variables and experimental design provide a background context for the statistical hypothesis testing that is described later in this document.

### Schedule of Visits and Measurements from Protocol



| | | | |
|---|---|---|---|
| [redacted] | [redacted] | | [redacted] |
| [redacted] | [redacted] | | [redacted] |
| [redacted] | | [redacted] | |
| [redacted] | | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | | [redacted] |

[redacted]

## 4.1 Efficacy Variables

The efficacy variable is as follows:

### 4.1.1 PRIMARY ENDPOINT:

- Ocular discomfort symptom score (0 [no discomfort] – 100 [maximal discomfort] VAS) over 100 minutes in the CAE at Visit 1 and Visit 3

## 4.2 Safety Variables

The safety variables include the following:

- Visual acuity
- Slit lamp examination
- Adverse event query
- Intraocular pressure

## 4.3 Estimands

[redacted]

[redacted]

1. The *population* is restricted to participants with dry eye disease who meet all the inclusion/exclusion criteria in the protocol and are included in the intent-to-treat (ITT) population. Dry eye disease patients are generally symptomatic across both eyes.

2. The *variable* constituting the primary endpoint is subject-reported ocular discomfort symptom score (0 – 100 VAS) over 100 minutes in the CAE at Visit 1 and Visit 3.

[redacted]

5. *Treatment:* There will be one active treatment arm (reproxalap) and one control arm (vehicle).

### 4.4 Statistical Hypothesis

The following hypothesis will be tested comparing reproxalap to vehicle. The null hypotheses must be rejected for the dosing regimen to claim efficacy.

[redacted]

## 5. Trial Design and Procedures

### 5.1 General Trial Design

ADX-102-DED-032 is a randomized, double-masked, vehicle-controlled, parallel-group clinical trial to assess efficacy and safety of reproxalap compared to vehicle in subjects with dry eye disease. The clinical trial will consist of 3 visits to the clinic over a period of approximately two weeks. Visit 1 will consist of screening and pre-CAE baseline (specific to Visit 1) assessments with response to vehicle in the CAE. Randomization will occur at Visit 2. Prior to randomization at Visit 2, a pre-dose baseline (specific to Visit 2 and Visit 3) assessment will be collected. After randomization at Visit 2, subjects will be administered four doses of randomized treatment outside the CAE. Visit 3 will consist of response to randomized treatment in the CAE. Statistical analyses are tailored to evaluate the impact of reproxalap under conditions that *facilitate* dry eye symptoms through the presence of the CAE (Visit 1 and Visit 3), and are designed to accommodate various sources of pre-specified variation such as time of collection, to provide error variation, and to provide within-subject statistical testing across repeated measures.

Trial visits will be referred to in all tables and listings as the scheduled Visit. The following table shows the scheduled trial visits, the planned trial 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 trial visit.

| Scheduled Visit | Planned Trial Day | Visit Window | Visit Description |
|---|---|---|---|
| Visit 1 | Day -14 | -14 TO -16 | Screening/CAE vehicle treatment visit |
| Visit 2 | Day 1 | N/A | Randomization/outside of CAE treatment visit |
| Visit 3 | Day 2 | N/A | CAE randomized treatment (reproxalap or vehicle) visit |

### 5.2 Schedule of Visits and Assessments

The schedule of visits and measurements is provided in 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

At Visit 1, each subject who signs the informed consent will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at each site and no numbers will be skipped or omitted.

At Visit 2, subjects who meets all eligibility criteria will be randomized to receive reproxalap or vehicle in a 1:1 ratio. Subjects will be assigned a randomization number and kit number via an interactive web response system.

The treatment assignment (reproxalap or vehicle) will be determined by randomization. [redacted] will generate the randomization scheme using standard operating procedures. Randomization of subjects will be based on the randomization scheme.

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

### 6.2 Masking and Unmasking

The statistical analysis will be performed without data alteration. The Sponsor, investigators, qualified site personnel, and subjects will be masked to the test article administered until database lock. Although statistical programming using data masked to treatment (i.e., using sham data) may occur prior to unmasking and data lock, the first unmasked analysis will occur after data lock.

All subjects, investigators, and study personnel involved with the conduct of the clinical trial will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (in non-emergent situations), [redacted] and/or the trial Sponsor will be notified before unmasking test article as described below.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, [redacted] and/or the medical monitor will be contacted prior to unmasking the identity of the test article. [redacted] will ask the site to complete and send the Unmasking Request Form. [redacted] will notify Aldeyra and jointly will determine if the unmasking request should be granted. The investigator may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject via the interactive web response system. The investigator will complete the Unmasking Memo form, will include the form in the subject study file, and will provide a copy of the form for the Trial Master File. For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject must be noted in the subject study file.

## 7. Sample Size and Power Considerations

[redacted]

## 8. Data Preparation

A trial chart/record will be maintained on-site for each subject, and will include records such as general observations, medical and medication use history, physical examination, and related documentation. The original record will be considered the data 'source document'. The source documents will be available for inspection in person or remotely by the study monitors and study monitor representatives before, during, or upon completion of the trial. Good documentation practices will be followed for source documentation. All corrections will be dated and initialed. The Investigator will retain original documents.

All clinical trial 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, and reported in compliance with the protocol, GCP standards, ICH, and other applicable local laws and regulations. All research staff will be appropriately trained to ensure the collection of accurate, consistent, complete,

and reliable data are entered onto an eCRF unique for each subject. All data collected in the trial will be captured and maintained in a secure and validated electronic data capture (EDC) system. Research staff will enter the data for each subject into the eCRF, with the exception of the data collected via an electronic or paper source (e.g., lab data, diary data, etc.). Data source will be described in the Data Management Plan.

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, which may occur in person or remotely. 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. Adverse events will be coded using a standard dictionary, Medical Dictionary for Regulatory Activities (MedDRA version 27.0 or higher), while concomitant medications will be categorized using the World Health Organization Drug Dictionary (the most updated version of the dictionary) at the start of the trial.

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 Data Management Plan, 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, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate 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]

[redacted]

#### 9.1.2 SUBGROUPS

Summary statistics for the primary efficacy endpoint will be provided for baseline and demographic characteristics such as iris pigmentation, age, gender, race, and ethnicity. The primary analysis model, as specified below, will be attempted; however, given small subgroup sample sizes, non-convergence may be expected.

### 9.2 Interim Analyses

No interim analyses are planned.

### 9.3 Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2) If the month is unknown, then:
   i) If the year matches the first dose date year, then impute the month and day of the first dose date.
   ii) Otherwise, assign ‘January.‘
3) If the day is unknown, then:
   i) If the month and year match the first dose date month and year, then impute the day of the first dose date.
   ii) Otherwise, assign the first day of the month.

B. Stop Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2) If the month is unknown, then assign ‘December.’
3) If the day is unknown, then assign the last day of the month.

Unless having an end date before the first administration of the study drug, an adverse event with a completely missing start date will be interpreted as started between the first dose date included and

recovery to a satisfactory state, or stabilization, or appropriate outcome is established as judged by the Investigator (included), or the analysis cut-off date included, whichever comes first.

A medication with a completely missing start date will be interpreted as started before the first dose date. A medication with a completely missing end date will be interpreted as ongoing at the time of data extraction (and therefore being not stopped before the first dose).

## 10. Analysis Populations

Analysis populations include the 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, separately, on the PP population as a sensitivity analysis.

### 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 who received at least one dose of test article, 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 test article. Subjects in the safety population will be analyzed as treated.

## 11. General Statistical Considerations

### 11.1 Unit of Analysis

Safety points will be analyzed for both eyes separately. Both eyes separately will be included in the statistical models that evaluate efficacy.

### 11.2 Missing or Inconclusive Data Handling

[redacted]

[redacted]

### 11.3 Baseline Definitions

[redacted]

## 12. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the trial, and discontinued from the trial. Subjects who are not discontinued from the trial will be considered trial completers. Disposition descriptive statistics, primary counts, and percentages will be summarized. Disposition information will be presented for the ITT population. In general, percentages will be calculated using randomized subjects as the denominator (with any exceptions noted).

The number and percentage of subjects prematurely discontinued from the trial and the reasons for trial discontinuation will be summarized for all randomized subjects. The reasons for trial discontinuation that will be summarized include adverse event, lost to follow-up, physician decision, protocol violation, study terminated by Sponsor, withdrawal by subject, and other. A subject listing will be provided that includes the date of and reason for premature trial discontinuation.

The number and percentage of subjects with major protocol deviations will be summarized by treatment 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 failure to report serious adverse event / adverse event, visit

out of window, subject non-compliance with test article, subject use of prohibited concomitant medication, subject failure to follow instructions, and other. A subject listing will include the date and description of each deviation. In addition, subject listings will include treatment arm, whether inclusion and exclusion criteria were met, and inclusion in the ITT, Safety, and PP populations.

## 13. Demographic, Baseline Characteristics, and Pretreatment Variables

### 13.1 Demographic Variables

The demographic and body habitus variables collected in this trial include age, sex, race, ethnicity, iris color, and childbearing potential and . These variables will be descriptively summarized, taking into account treatment arm, for the ITT and safety populations, separately.

Age (years) will be summarized using continuous descriptive statistics. Further, age will be categorized as <65 years or ≥65 years. Age will be reported in years and calculated using the following formula:

Age = (informed consent date – date of birth) / 365.25 truncated as an integer

The number and percentage of subjects will be presented for age category, sex, race, ethnicity, iris color by eye (OD and OS, separately), and for childbearing potential.

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

### 13.2 Baseline Characteristics

A baseline characteristics table will include descriptive summary statistics for various baseline characteristics for each eye in the ITT and/or safety population. Baseline data for the primary endpoint, staining, and other variables may be included. Other summary methods, such as area under the curve (AUC) or averages for 80 min to 100 min, may be included.

### 13.3 Pretreatment Variables

Baseline intraocular pressure and visual acuity will be summarized with descriptive statistics for all subjects by eye. Subjects will be grouped by treatment arm.

## 14. Medical History and Concomitant Medications

### 14.1 Medical History

Medical history will be coded using MedDRA Version 27.0 or higher.

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 WHODrug Global, B3, March 2024 (or higher) 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."

Prior medications are defined as those medications listed as having an end date prior to Visit 1.

Concomitant medications are defined as those medications listed as having been taken 1) prior to Visit 1 and continuing for any period of time following Visit 1, or 2) at any time following Visit 1.

Concomitant medications will be summarized using the ITT population by treatment arm. 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 one medication per ATC text. At each level of subject summarization, a subject will be counted once if that subject reports one or more medications. Percentages will be based on the number of subjects in each treatment condition. Listings of prior and 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 trial; 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 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 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. Descriptive statistics for exposure will be presented by treatment arm for overall exposure, exposure prior to Day 1 and exposure after Day 1.

## 16. Efficacy Analyses

### 16.1 Analysis of the Primary Efficacy Endpoint

The primary endpoint will be assessed using the ITT population with observed data only. The ITT population includes all randomized subjects.

[redacted]

[redacted]

### 16.2 Analysis of the Secondary Endpoints

Not applicable.

### 16.3 Model Presentation

[redacted]

### 16.4 Covariance Structures and Convergence

[redacted]

### 16.5 Efficacy Criterion

[redacted]

### 16.6 Multiplicity Considerations

Not applicable

## 17. Safety Analysis

All safety analyses will be conducted using the safety population.

### 17.1 Adverse Events

An adverse event is defined as any untoward medical occurrence associated with the use of an test article in humans, whether or not considered test-article-related. An adverse event can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of test article, without any judgment about causality. Exacerbation of conditions related to the signs and symptoms of dry eye disease will not be reported as an adverse event. The adverse event reporting period ends upon trial exit. Study drug includes the investigational drug under evaluation.

All adverse events will be coded using MedDRA Version 27.0 (or higher).

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

An overall summary will be presented that includes the number and percentage of subjects who experienced at least one AEs, ocular AEs, non-ocular AEs, SAEs, AEs by maximal severity, AEs by relationship to study procedure, AEs leading to treatment discontinuation, and AEs resulting in death by treatment arm for the Safety Population. In addition, overall TEAEs and the number and percentage of subjects who experienced at least one TEAE, ocular TEAEs, non-ocular TEAEs, TE-SAEs, TEAEs by maximal severity, TEAEs by relationship to study procedure, TEAEs leading to treatment discontinuation, and TEAEs resulting in death by treatment arm for the Safety Population.

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

- Ocular AEs by SOC and PT
- Non-ocular AEs by SOC and PT

- Ocular TEAEs by SOC and PT
- Non-ocular TEAEs by SOC and PT
- Instillation Site Ocular TEAEs by Duration of Time
- Ocular TEAEs by SOC, PT, and maximal severity
- Non-ocular TEAEs by SOC, PT, and maximal severity
- Ocular TEAEs by SOC, PT, and strongest relationship to study procedure
- Non-ocular TEAEs by SOC, PT, and strongest relationship to study procedure
- Ocular TEAEs by SOC, PT, maximal severity, and strongest relationship to study procedure
- Non-ocular TEAEs by SOC, PT, maximal severity, and strongest relationship to study procedure
- TEAEs That Led to Premature Treatment Discontinuation
- SAEs

Adverse Events and TEAEs will be summarized using discrete summary statistics and presented by treatment arm and all subjects for the the Safety Population. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs will be listed in ascending alphabetical order. PTs will be listed in order of descending frequency within each SOC for all subjects.

A missing severity will be considered Severe. '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'.

All AEs, ocular AEs, non-ocular AEs, and SAEs will be presented in subject listings.

## 18. Other Safety Variables

### 18.1 Visual Acuity (ETDRS)

Visual acuity will be performed pre-CAE (and pre symptom assessment) and again at post-CAE exposure. The logarithm of the minimum angle of resolution (logMAR) visual acuity 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.

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 visual acuity 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-CAE (and pre symptom assessment) and again at post-CAE 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. A subject listing of the slit lamp biomicroscopy parameters will also be produced.

### 18.3 Intraocular Pressure

Intraocular pressure will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg. Intraocular pressure will be performed post--CAE exposure. A single measurement is made to obtain a determination of intraocular pressure. The same tonometer employing the investigator's standard technique will be used throughout the trial. In addition, all reasonable efforts will be made to have the same examiner obtain all intraocular pressure measurements for a given subject.

The Intraocular pressure 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 intraocular pressure also will be produced.

## 19. Additional Analyses

Additional analyses for the purpose of sensitivity assessment, hypothesis generation, and improved understanding of the treatment effect be conducted as ad-hoc analyses. All ad-hoc analyses will be identified in the CSR.

Sensitivity analyses for the primary analysis will include the following:

- A MMRM with Visit 3 ocular discomfort score as the dependent variable (compared at the same time points specified for the primary endpoint analysis [80 min to 100 min]); the Visit 3 baseline (pre-Dose 1 at Visit 2), the year of dry eye disease diagnosis (e.g., 1997), the time point-matched Visit 1 scores, and the average and standard deviation of all ocular discomfort scores from Visit 1 as covariates; and time (10 min to 100 min), treatment arm, and month of Visit 1 as factors, with correlated errors due to eye and time point; and

- Observed data only using the PP population.

Additional sensitivity analyses with time point removed from the primary model may be run by time point.

## 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 trial 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 trial, 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) at the top of each output, 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 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