STATISTICAL ANALYSIS PLAN

A Multi-Center Randomized, Double-Masked, Parallel Design, Vehicle-Controlled Phase 2 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-024

Author: [redacted]

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Protocol Number: **ADX-102-DED-024**

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Statistical Analysis Plan Approval

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List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
CAC	Conjunctival Allergen Challenge
CAE®	Controlled Adverse Environment®
CI	Confidence Interval
CS	Clinically Significant
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MNAR	Missing Not at Random
NCS	Not Clinically Significant
OD	*Oculus dexter* (Right Eye)
OS	*Oculus sinister* (Left Eye)
PDF	Portable Document Format
PMM	Pattern Mixture Model
PP	Per Protocol
PT	Preferred Term
RASP	Reactive Aldehyde Species
RDC	Remote Data Capture
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TMF	Trial Master File
VAS	Visual Analog Scale

WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol ADX-102-DED-024, version 2.0, dated 12OCT2021.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

To evaluate the efficacy of reproxalap, as assessed by conjunctival redness, tear RASP levels, Schirmer's Test, and symptoms after dosing prior to and during exposure to the Controlled Adverse Environment® (CAE) in subjects with dry eye disease.

3. Study Endpoints

3.1 Primary Endpoint

The primary efficacy endpoint is comprised of the following:

- Conjunctival redness [redacted]
- Visual analog scale (VAS) [redacted]
- Schirmer's test [redacted]

3.2 Secondary Endpoints

The secondary efficacy endpoints are the following:

- Visual analog scale (VAS) eye dryness score [redacted]
- Ora Calibra® Ocular Discomfort Scale [redacted]
- Ocular Discomfort & 4-Symptom Questionnaire [redacted]
- Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale [redacted] redness [redacted]

[redacted]

at Visit 3 in the ITT population using observed data only. The following estimand will be used for the primary analysis of the

primary endpoint of overall mean change from baseline [redacted]

Estimand 1

- Population: subjects with DED, defined through enrollment criteria
- Endpoint:
  - Overall mean change from baseline in conjunctival redness in each eye [redacted]
  - Overall mean change from baseline in eye dryness [redacted]
  - Mean change from baseline in Schirmer's test [redacted]
- Intercurrent events:
  - [redacted]
- Population-level summary:
  - Difference in the overall mean change from baseline in conjunctival redness in [redacted]
  - Difference in the overall mean change from baseline in eye dryness [redacted]
  - Difference in the mean change from baseline in Schirmer's test [redacted]

4. Study Design and Procedures

4.1 General Study Design

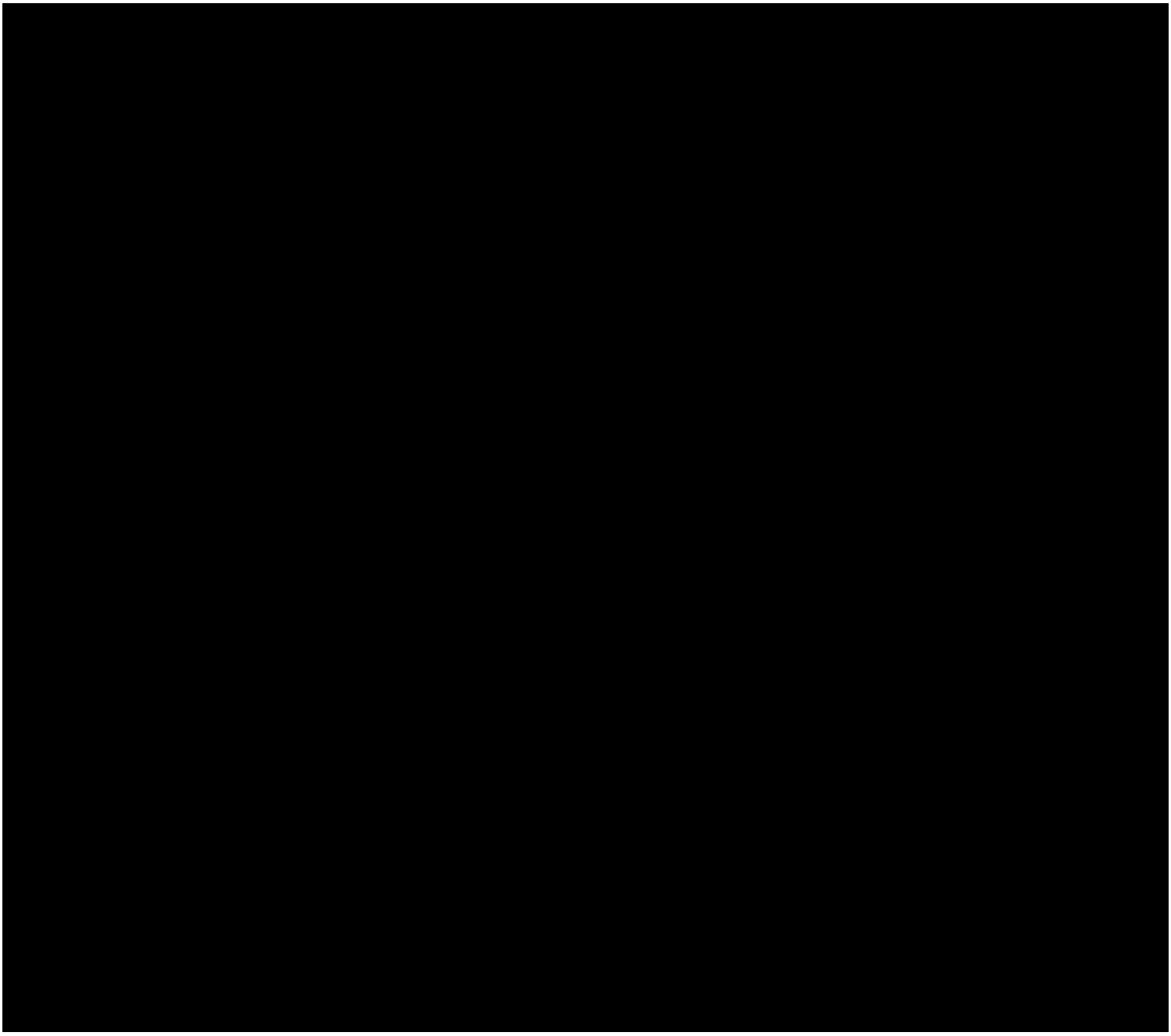
Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Table 1 shows the scheduled study visits, their planned study day (note that there is no Day 0 and that Day 1 corresponds to the day of randomization), and the acceptable visit window for each study visit:

Table 1. Study Visit Windows

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -14	-16/+2 days
Visit 2	Day 1	N/A
Visit 3	Day 2	N/A

4.2 Schedule of Visits and Assessments

Table 2. Schedule of Visits and Assessments



5. Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

At Visit 1 (Day -14), 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 (Day 1), a subject who meets all the eligibility criteria will be randomized in a 1:1 ratio to receive treatment with either 0.25% Reproxalap Ophthalmic Solution or placebo. Subjects will be assigned a randomization number and kit number via paper randomization list for the Initial Cohort and by interactive web response system (IWRS) for the Main Cohort.

The site staff will dispense to the subject the study kit labeled with the corresponding kit number. Both the randomization number and the dispensed study drug kit number will be recorded on the subject's source document and electronic case report form (eCRF).

5.2 Masking and Unmasking

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study Sponsor should be notified, when possible, before unmasking study drug as described in the following paragraph.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact Ora and/or the medical monitor prior to unmasking the identity of the IP, if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify Aldeyra and jointly will determine if the unmasking request should be granted. They 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 scratch-off labels on the kits for the Initial Cohort Only. The investigator will unmask the subject using IWRS for the Main Cohort. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the Trial Master File (TMF). For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject must be noted in the subject's study file.

6. Sample Size and Power Considerations

[redacted]

[redacted]

7. Data Preparation

7.1 Input Data

Study data will primarily be recorded on the eCRFs supplied by Statistics & Data Corporation (SDC) using [redacted]). [redacted] is delivered as a single-instance, multi-tenant Software-as-a-Service (SaaS) EDC system and is developed, maintained, and hosted by [redacted]. These data sources are described in detail in data transfer agreements developed between data management and the respective external laboratory or reading center:

- Tear RASP data
- Conjunctival redness photography scores

When all prerequisites for database lock have been met, including availability of all masked external data, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study. Once the study has been unmasked, unmasked laboratory data will be sent to SDC. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

Final analysis will be carried out after the following have occurred:

- Database lock has occurred, including receipt of all final versions of external vendor data, with written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

7.2 Output Data

Data from EDC and external data will be transferred to SDC Biostatistics and incorporated into standard formats [redacted]). Data will then be mapped to analysis datasets using the [redacted] Both [redacted] will be used to create the subject listings, while all tables and figures will be based on the [redacted]

SDTM will follow the [redacted] and will be implemented using the [redacted] most current at the time of study start. [redacted] data will follow the [redacted] and will be implemented using the [redacted]

Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

[redacted]

8. Analysis Populations

8.1 Intent-to-Treat

The Intent-to-Treat (ITT) Population includes all randomized subjects. Subjects in the ITT Population will be analyzed as randomized.

8.2 Per Protocol

The Per-Protocol (PP) Population includes subjects in the ITT Population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP Population will be analyzed as treated.

8.3 Safety

The Safety Population includes all randomized subjects who receive at least one dose of investigational product. [redacted].

9. General Statistical Considerations

9.1 Unit of Analysis

Safety endpoints will be analyzed for both eyes [redacted] will be made on [redacted] samples pooled [redacted] resulting in a single measurement for each subject and time point. Conjunctival redness, Schirmer's Test, and ocular discomfort scores from the Ora Calibra Ocular Discomfort Scale will be collected and analyzed for each eye. Eye dryness from the Visual Analog Scale (VAS) and Ocular Discomfort & 4-Symptom Questionnaire scores will be collected at the subject level [redacted] Ocular itching from the Ora Calibra® Conjunctival Allergen Challenge will be collected in both eyes and analyzed [redacted]. Assessment scales are detailed in the appendices of the study protocol.

9.2 Missing or Inconclusive Data Handling

Partial/missing start and end dates for AEs and concomitant medications required to flag data as treatment-emergent or concomitant with treatment will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or "Yes" then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is "No" then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc).

[redacted]

9.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study treatment, [redacted] Change from baseline will be calculated as post-baseline measurement – baseline measurement.

9.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed [redacted]. Output will be provided [redacted] for tables and [redacted] All study data will be listed by subject, treatment, and visit (as applicable) based on [redacted].

Summaries for continuous and ordinal variables will include [redacted]

All statistical tests will be [redacted]

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit. Listings will be sorted by subject number, visit/time point, and parameter as applicable.

9.5 Adjustments for Multiplicity

[redacted]

Step	Endpoint	Allocated Two-sided Alpha Level
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted] Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized who were included in the following analysis populations: ITT, PP, and Safety; and who completed the study and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all subjects. Percentages will be calculated using randomized subjects as the denominator unless otherwise specified.

The reasons for premature study discontinuation will be summarized by treatment group for all discontinued subjects. Percentages will be calculated using discontinued subjects as the denominator. The reasons for study discontinuation that will be summarized include AE(s), protocol violation(s), administrative reasons, Sponsor termination of study, subject choice, and other. COVID-19 related discontinuations will be summarized similarly by treatment group as well. A subject listing will be provided that includes the date of discontinuation, reason for study discontinuation, and an indication of COVID-19 relatedness with a description.

The number and percentage of subjects with any deviation, major deviation, and minor deviation will be summarized by treatment group for all randomized subjects. The protocol deviations that will be summarized include the following categories: [redacted] A subject listing will be provided that includes the visit, date of the deviation,

the deviation category, the deviation description, and the classification of whether the deviation was judged to be major or minor in a masked review. [redacted]

Subject listings will be provided that include randomization information such as randomization number, treatment group, and date. Listings will also be provided to include subject data for inclusion and exclusion criteria violations and exclusions from the study populations. [redacted]

11. Demographic, Previous Participation in Reproxalap Trials, and Pretreatment Variables

11.1 Demographic Variables

The demographic variables collected in this study include [redacted] Subjects who record [redacted]

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized [redacted] 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, [redacted]

A subject listing that includes all demographic variables, including informed consent, will be provided.

11.2 Previous Participation in Reproxalap Trials

The number of subjects and percentages of subjects that dosed with randomized study drug in previous Reproxalap trials will be summarized by treatment group and for all subjects in the ITT population.

[redacted]

Subjects who did not dose under previous Reproxalap studies will be summarized as well.

11.3 Pretreatment Variables

All baseline efficacy and safety variables will be summarized by eye (or subject level) by treatment group and all randomized subjects. [redacted]

[redacted] Quantitative variables will be summarized by using descriptive statistics with qualitative variables summarized by counts and percentages. Summaries will be provided of the ITT and Safety Populations.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1.

[redacted]

Listings of medical history will be generated separately for [redacted]

12.2 Concomitant Medications and Procedures

Concomitant medications and procedures will be coded using World Health Organization Drug Dictionary (WHODrug) [redacted] and summarized to the therapeutic drug class [redacted] and preferred name. If the [redacted] is not provided, then 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 [redacted]

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. Prior medications are defined as those medications as having been taken prior to initiation of study drug administration but not continuing any time following the first administration of study drug.

Concomitant medications will be summarized [redacted]. Medications will be tabulated for each treatment group using frequencies and percentages. [redacted] At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated separately for ocular and non-ocular data.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

Dosing compliance [redacted] will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

[redacted]

The number of actual doses received will be calculated from in-office instillation eCRF page. [redacted]

Dosing compliance (%) will be summarized [redacted] The compliance category defined above will be summarized with discrete summary statistics.

A subject listing of dosing compliance will also be produced.

13.2 Treatment Exposure

Extent of treatment exposure for subjects who complete the study or those that discontinue the study [redacted]

Extent of treatment exposure for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group [redacted] A subject listing of treatment exposure will also be produced.

14. Efficacy Analyses

All efficacy analyses described in this section will have [redacted]

14.1 Primary Analysis

The primary endpoint will be deemed to have been met if any of the 3 assessments that comprise the primary endpoint are achieved, as is described [redacted]

14.1.1 Overall Mean Change from Baseline of Conjunctival Redness During the CAE at Visit 3 (Day 2)

The endpoint of overall mean change from baseline [redacted]

[redacted]

These average scores for each separate eye will be used for analysis of the overall mean change from baseline of conjunctival redness. [redacted]

14.1.1.1 Mixed Model Repeated Measures using Scores from Each Eye

Overall mean change from baseline [redacted] will be compared between reproxalap and vehicle. [redacted]

met, then the trial will have been deemed to have been successful in demonstrating sign activity of reproxalap.

14.1.1.2 Mixed Model Repeated Measures using Average Scores from Each Eye

[redacted]

14.1.1.3 Additional Sensitivity Analyses

[redacted]

- [redacted]
- [redacted]

To examine the robustness of the redness analysis, the following additional sensitivity analyses will be executed:

- [redacted]
- [redacted]

14.1.2 Overall Mean Change from Baseline of Eye Dryness Score [redacted]

Subjects will be asked to rate eye dryness [redacted]

[redacted]

[redacted]

A subject listing of the eye dryness during the CAE will be generated.

14.1.2.1 Additional Sensitivity Analyses

[redacted]

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

14.1.3 Mean Change from Baseline of Unanesthetized Schirmer's Test

Unanesthetized Schirmer's test will be assessed for each eye. [redacted]

14.1.3.1 Mixed Model Repeated Measures Using Scores From Each Eye

Mean CFB of unanesthetized Schirmer's test [redacted]

A subject listing of the unanesthetized Schirmer's test will be generated.

14.1.3.2 Additional Sensitivity Analyses

Additional sensitivity analyses of the endpoint of mean change from baseline of unanesthetized Schirmer's test [redacted]

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

14.2 Secondary Analyses

14.2.1 Conjunctival Redness (ORA Calibra® Scale) [redacted]

The overall mean CFB of the conjunctival redness [redacted]

Analyses will use the ITT Population with observed data only. A subject listing of the conjunctival redness outside of the CAE® will be generated.

14.2.2 Eye Dryness Score from the Visual Analog Scale [redacted]

[redacted]

[redacted]

Analyses will use the ITT Population with observed data only. A subject listing of the eye dryness outside of the CAE® will be generated.

14.2.3 Ocular Discomfort Scale (ORA Calibra® Scale)

Ocular Discomfort will be assessed [redacted]

14.2.3.1 Ocular Discomfort Scale (ORA Calibra® Scale) [redacted]

[redacted] A subject listing of the Ocular Discomfort Scale outside of the CAE® will be generated.

14.2.3.2 Overall Mean Change From Baseline of Ocular Discomfort Scale (ORA Calibra® Scale) [redacted]

[redacted] A subject listing of the Ocular Discomfort Scale during the CAE® will be generated.

14.2.4 Ocular Discomfort & 4-Symptom Questionnaire (ORA Calibra® Scale)

[redacted]

14.2.4.1 Ocular Discomfort & 4-Symptom Questionnaire (ORA Calibra® Scale)

[redacted] A subject listing of the Ocular Discomfort & 4-Symptom Questionnaire will be generated.

14.2.4.2 Ocular Discomfort & 4-Symptom Questionnaire (ORA Calibra® Scale)

[redacted] A subject listing of the Ocular Discomfort & 4-Symptom Questionnaire will be generated.

14.2.5 Conjunctival Allergen Challenge Ocular Itching Scale (ORA Calibra® Scale)

[redacted]

14.2.5.1 Conjunctival Allergen Challenge Ocular Itching Scale (ORA Calibra® Scale)

[redacted]

[redacted] A subject listing of the Conjunctival Allergen Challenge Ocular Itching Scale will be generated.

14.2.5.2 Conjunctival Allergen Challenge Ocular Itching Scale (Ora Calibra® Scale)

[redacted]

14.3 Exploratory Analyses

14.3.1 Tear Reactive Aldehyde Species

[redacted]

Tears will be collected from both eyes. [redacted]

[redacted] A subject listing of the tear RASP will be generated.

14.3.2 Conjunctival Redness (Ora Calibra® Scale)

[redacted]

For conjunctival redness [redacted]

14.3.3 Eye Dryness (VAS)

[redacted]

[redacted]

14.3.4 Ocular Discomfort Scale (ORA Calibra® Scale) [redacted]

[redacted]

15. Summary of Efficacy Analyses

A summary of all efficacy analyses will be presented. [redacted]

[redacted]

16. Safety Analyses

All safety analyses will be conducted using the Safety Population [redacted].

16.1 Adverse Events

For the purposes of this trial, an AE is defined as any untoward medical event occurring after the subject's signing of the informed consent until they are exited from the trial. An AE can therefore be any unfavorable and unintended sign, symptom, or disease occurring after the subject started the clinical trial, without any judgment about causality. Any pre-existing medical condition that worsens during the trial will also be considered a new AE. Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study procedure, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the investigator or reported by the patient upon indirect questioning.

All AEs will be coded using the MedDRA Version 23.1.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated. 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 AE 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 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.

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

16.1.1 SEVERITY

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to them by the patient/subject. The assessment of severity is made irrespective of relationship to study procedures or seriousness of the event and should be evaluated according to the following scale:

- [redacted]

- [redacted]
- [redacted]

Subjects experiencing more than one AE within a given SOC or PT are counted once within that SOC or PT for the maximal severity.

16.1.2 Relationship to Study Procedures

The relationship of each AE to the study procedures should be determined by the investigator using these explanations. Decisive factors for the assessment of causal relationship of an AE to the study procedures include, but may not be limited to, temporal relationship between the AE and the procedure, known side effects of the procedure medical history, and/or concomitant medication:

- Definite: When there are good reason and sufficient documentation to demonstrate a direct causal relationship between study procedure and AE;
- Probable: When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable.
- Possible: When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example; due to missing data or insufficient evidence.
- None: When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- Unclassified: When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

Subjects experiencing more than one AE within a given SOC or PT are counted once within that SOC or PT for the maximum relationship.

16.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the study procedures. Therefore, the following definition will be used:

- Unexpected: An AE that is not listed in the safety information available for the study procedure at the specificity or severity that has been observed.
- Expected: An AE that is listed in the safety information available for the study procedure at the specificity and severity that has been observed.
- Not Applicable: Any AE that is unrelated to the study procedure.

16.1.4 SERIOUS ADVERSE EVENTS

An AE is considered serious if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
    - Note: An adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;
    - Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.
    - Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
    - Note: A serious adverse event specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).
- A congenital anomaly/birth defect.

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

16.2 Visual Acuity (Early Treatment Diabetic Retinopathy Study)

The logarithm of the minimum angle of resolution (logMAR) visual acuity is assessed at each visit [redacted]

[redacted] A subject listing of visual acuity will also be produced.

16.3 Slit-Lamp Biomicroscopy

A slit-lamp biomicroscopy [redacted] will be performed [redacted] A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

16.4 Dilated Fundoscopy Examination

A dilated fundoscopy examination [redacted] will be performed [redacted] A subject listing of the dilated fundoscopy parameters will also be produced.

16.5 Intraocular Pressure (IOP)

Subjects' IOP will be assessed [redacted]. A subject listing of IOP will also be produced.

17. Changes from Protocol-Stated Analyses

No changes to protocol-stated analyses will be executed.

18. References

No references cited.

19. Revision History

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

20. Tables

Tables (10 tables) in **boldface** font will be delivered in topline package.

Table Number	Title	Population

Table 14.1.1	Subject Disposition	All Screened Subjects
Table 14.1.2.1	Demographics	ITT Population
Table 14.1.2.2	Demographics	Safety Population
Table 14.1.2.3	Previous Participation in Reproxalap Trials	ITT Population
Table 14.1.3.1	Baseline Disease Characteristics	ITT Population
Table 14.1.3.2	Baseline Disease Characteristics	Safety Population
Table 14.1.4.1	Ocular Medical History	ITT Population
Table 14.1.4.2	Non-Ocular Medical History	ITT Population
Table 14.1.5.1	Ocular Concomitant Medications	ITT Population
Table 14.1.5.2	Non-Ocular Concomitant Medications	ITT Population
Table 14.2.1.1	**Overall Mean Change from Baseline of Conjunctival Redness (Ora Calibra® Scale)** [redacted]	**ITT Population with Observed Data Only**
Table 14.2.1.2	Overall Mean Change from Baseline of Conjunctival Redness (Ora Calibra® Scale) [redacted]	PP Population with Observed Data Only
Table 14.2.1.3	Overall Mean Change from Baseline of Conjunctival Redness (Ora Calibra® Scale) [redacted]	ITT Population with Observed Data Only
Table 14.2.1.4	Overall Mean Change from Baseline of Conjunctival Redness (Ora Calibra® Scale) [redacted]	ITT Population with Observed Data Only
Table 14.2.1.5	Overall Mean Change from Baseline of Conjunctival Redness (Ora Calibra® Scale) [redacted]	ITT Population with PMM
Table 14.2.1.6	Overall Mean Change from Baseline of Conjunctival Redness (Ora Calibra® Scale) [redacted]	ITT Population with MCMC
Table 14.2.2.1	**Overall Mean Change from Baseline of Eye Dryness (Visual Analog Scale)** [redacted]	**ITT Population with Observed Data Only**

Table 14.2.2.2	Overall Mean Change from Baseline of Eye Dryness (Visual Analog Scale) [redacted]	PP Population with Observed Data Only
Table 14.2.2.3	Overall Mean Change from Baseline of Eye Dryness (Visual Analog Scale) [redacted]	ITT Population with PMM
Table 14.2.2.4	Overall Mean Change from Baseline of Eye Dryness (Visual Analog Scale) [redacted]	ITT Population with MCMC
Table 14.2.3.1	**Mean Change from Baseline of Unanesthetized Schirmer's Test** [redacted]	**ITT Population with Observed Data Only**
Table 14.2.3.2	Mean Change from Baseline of Unanesthetized Schirmer's Test [redacted]	PP Population with Observed Data Only
Table 14.2.3.3	Mean Change from Baseline of Unanesthetized Schirmer's Test [redacted]	ITT Population with PMM
Table 14.2.3.4	Mean Change from Baseline of Unanesthetized Schirmer's Test [redacted]	ITT Population with MCMC
Table 14.2.4.1	**Conjunctival Redness (Ora Calibra® Scale)** [redacted]	**ITT Population with Observed Data Only**
Table 14.2.4.2	**Eye Dryness (Visual Analog Scale)** [redacted]	**ITT Population with Observed Data Only**
Table 14.2.4.3	**Ocular Discomfort Scale (Ora Calibra® Scale)** [redacted]	**ITT Population with Observed Data Only**
Table 14.2.4.4	**Overall Mean Change from Baseline of Ocular Discomfort Scale (Ora Calibra® Scale)** [redacted]	**ITT Population with Observed Data Only**
Table 14.2.4.5	Ocular Discomfort & Four-Symptom Questionnaire (Ora Calibra® Scale) [redacted]	ITT Population with Observed Data Only
Table 14.2.4.6	Ocular Discomfort & Four-Symptom Questionnaire (Ora Calibra® Scale) [redacted]	ITT Population with Observed Data Only

Table 14.2.4.7	Conjunctival Allergen Challenge Ocular Itching Scale (Ora Calibra® Scale) [redacted]	ITT Population with Observed Data Only
Table 14.2.4.8	Conjunctival Allergen Challenge Ocular Itching Scale (Ora Calibra® Scale) [redacted]	ITT Population with Observed Data Only
Table 14.2.5.1	Tear Reactive Aldehyde Species – [redacted]	ITT Population with Observed Data Only
Table 14.2.5.2	Conjunctival Redness (Ora Calibra® Scale) [redacted]	ITT Population with Observed Data Only
Table 14.2.5.3	Eye Dryness (Visual Analog Scale) [redacted]	ITT Population with Observed Data Only
Table 14.2.5.4	Ocular Discomfort Scale (Ora Calibra® Scale) [redacted]	ITT Population with Observed Data Only
Table 14.2.6	Summary of Efficacy Analyses	Multiple Populations
Table 14.3.1.1	**Overall Summary of Adverse Events by Treatment Arm**	**Safety Population**
Table 14.3.2.1	Ocular Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2	Non-Ocular Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.3.1	**Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**	**Safety Population**
Table 14.3.3.2	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.4	Instillation Site Ocular TEAEs by SOC, PT, and Duration of Time	Safety Population
Table 14.3.5.1	Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximal Severity	Safety Population
Table 14.3.5.2	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximal Severity	Safety Population

Table 14.3.6.1	Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Strongest Relationship to Study Procedure	Safety Population
Table 14.3.6.2	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Strongest Relationship to Study Procedure	Safety Population
Table 14.3.7.1	Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Maximal Severity, and Strongest Relationship to Study Procedure	Safety Population
Table 14.3.7.2	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Maximal Severity, and Strongest Relationship to Study Procedure	Safety Population
Table 14.3.8	Treatment-Emergent Adverse Events That Led to Premature Discontinuation	Safety Population
Table 14.3.9	Treatment-Emergent Serious Adverse Events	Safety Population
Table 14.3.10	Visual Acuity [redacted]	Safety Population
Table 14.3.11.1	Slit Lamp Biomicroscopy	Safety Population
Table 14.3.11.2	Shift in Slit Lamp Biomicroscopy	Safety Population
Table 14.3.12	Intraocular Pressure [redacted]	Safety Population
Table 14.3.13.1	Dilated Fundoscopy	Safety Population
Table 14.3.13.2	Shift in Dilated Fundoscopy	Safety Population
Table 14.3.14	Compliance to Study Drug	Safety Population
Table 14.3.15	Exposure to Study Drug	Safety Population

21. Listings

Listing Number	Title	Population
Listing 16.1.7	Randomization Schedule	All Randomized Subjects

Listing 16.2.1.1	Subject Disposition	All Randomized Subjects
Listing 16.2.1.2	Inclusion/Exclusion and Screen Failure	All Screened Subjects
Listing 16.2.2	Protocol Deviations	All Screened Subjects
Listing 16.2.3.1	Study Population Inclusion	All Randomized Subjects
Listing 16.2.3.2	Subjects Affected by COVID-19	All Screened Subjects
Listing 16.2.4.1	Demographics	All Screened Subjects
Listing 16.2.4.2	Ocular Medical History	All Randomized Subjects
Listing 16.2.4.3	Non-Ocular Medical History	All Randomized Subjects
Listing 16.2.4.4	Ocular Concomitant Medications	All Randomized Subjects
Listing 16.2.4.5	Non-Ocular Concomitant Medications	All Randomized Subjects
Listing 16.2.5.1	Run-In Instillation	All Screened Subjects
Listing 16.2.5.2	Study Drug Assignment, Instillation, and Replacement	All Randomized Subjects
Listing 16.2.5.3	Study Drug Exposure and Dosing Compliance	All Randomized Subjects
Listing 16.2.5.4	Study Drug Accountability	All Randomized Subjects
Listing 16.2.6.1	Conjunctival Redness (Ora Calibra Scale) [redacted]	All Randomized Subjects
Listing 16.2.6.2	Conjunctival Redness (Ora Calibra Scale) [redacted]	All Randomized Subjects
Listing 16.2.6.3	Unanesthetized Schirmer's Test	All Randomized Subjects
Listing 16.2.6.4	Eye Dryness (Visual Analog Scale) [redacted]	All Randomized Subjects

Listing 16.2.6.5	Eye Dryness (Visual Analog Scale) [redacted]	All Randomized Subjects
Listing 16.2.6.6	Ocular Discomfort Scale (Ora Calibra Scale) [redacted]	All Randomized Subjects
Listing 16.2.6.7	Ocular Discomfort Scale (Ora Calibra Scale) [redacted]	All Randomized Subjects
Listing 16.2.6.8	Ocular Discomfort & 4-Symptom Questionnaire (Ora Calibra Scale)	All Randomized Subjects
Listing 16.2.6.9	Conjunctival Allergen Challenge Ocular Itching Scale (Ora Calibra Scale)	All Randomized Subjects
Listing 16.2.6.10	Tear Reactive Aldehyde Species	All Randomized Subjects
Listing 16.2.6.11	Fluorescein Corneal and Conjunctival Staining (Ora Calibra Scale)	All Randomized Subjects
Listing 16.2.7.1	All Adverse Events	All Screened Subjects
Listing 16.2.7.2	Ocular Adverse Events	All Screened Subjects
Listing 16.2.7.3	Non-Ocular Adverse Events	All Screened Subjects
Listing 16.2.7.4	Serious Adverse Events	All Screened Subjects
Listing 16.2.8.1	Visual Acuity [redacted]	All Randomized Subjects
Listing 16.2.8.2	Slit-Lamp Biomicroscopy	All Randomized Subjects
Listing 16.2.8.3	Intraocular Pressure (IOP)	All Randomized Subjects
Listing 16.2.8.4	Dilated Fundoscopy	All Randomized Subjects
Listing 16.2.8.5	Pregnancy Test	All Female Screened Subjects
Listing 16.2.8.6	Tear Collection	All Randomized Subjects