STATISTICAL ANALYSIS PLAN

A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Environmental Clinical Trial with Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in Subjects with Seasonal Allergic Conjunctivitis

Sponsor: Aldeyra Therapeutics, Inc.
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Protocol Number: ADX-102-AC-010

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Statistical Analysis Plan Approval

[redacted]

Prepared by:

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List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ACQLQ	Allergic Conjunctivitis Quality of Life Questionnaire
AR1	Autoregressive 1 (covariance structure)
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
AUC_{t1-t2}	Area Under the Curve [redacted]
CAC	Conjunctival Allergen Challenge
CRF	Case Report Form
CI	Confidence Interval
CS	Clinically Significant
CS	Compound Symmetric (covariance structure)
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
GEE	Generalized Estimating Equation
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
NCS	Not clinically significant
PDF	Portable Document Format
PP	Per Protocol
PRN	As Needed
PT	Preferred Term
QID	Four Times Daily
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TOEP	Toeplitz (covariance structure)
VA	Visual Acuity

WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol ADX-102-AC-010, Version 2.0 dated 24AUG2018.

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 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 as post hoc analyses and will be identified in the clinical study report as such.

2. Study Objectives

The exploratory objectives of this study are the following:

- Evaluate the feasibility of a novel, [redacted] dosing regimen of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in an environmental clinical trial design.
- Evaluate the efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) on the signs and symptoms associated with seasonal allergic conjunctivitis during allergy season in an environmental clinical trial design that utilizes a daily diary.
- Evaluate the safety of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in an environmental clinical trial design.

3. Study Variables

3.1 Exploratory Efficacy Variables

The exploratory efficacy endpoints are the following:

- [redacted] ocular itching scores [redacted]
- [redacted] ocular redness scores [redacted]
- [redacted]

- [redacted] assessments for eyelid swelling and tearing/watery eyes [redacted]
- Assessments [redacted]:
  - Ocular redness [redacted];
  - Ocular itching [redacted];
  - Ocular redness [redacted]
  - Eyelid swelling [redacted]
  - Tearing/watery eyes [redacted].
- Allergic Conjunctivitis Quality of Life Questionnaire (ACQLQ) [redacted]

3.2 Safety Variables

The safety variables include the following:

- Adverse Events (AE) (reported, elicited, and observed);
- Visual Acuity (VA) [redacted]
- Slit-lamp Biomicroscopy;
- Intraocular Pressure (IOP);
- Dilated Fundoscopy.

3.3 Statistical Hypotheses

This early phase (1b), exploratory clinical trial is designed to assess the safety, tolerability, and pharmacodynamic activity of Reproxalap Ophthalmic Solution. Consequently, there are no primary endpoints and no formal statistical hypotheses.

4. Study Design and Procedures

4.1 General Study Design

This is a multi-center, double-masked, randomized, parallel-group, vehicle-controlled, Phase 1b methods environmental clinical trial to evaluate Reproxalap Ophthalmic Solution (0.25%) and Reproxolap Ophthalmic Solution (0.5%) compared to Vehicle Ophthalmic Solution in subjects with seasonal allergic conjunctivitis. [redacted]

Subjects will sign the informed consent form at Visit 1 [redacted] and will undergo an allergic skin test [redacted]. At Visit 2 [redacted] each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration [redacted]. Subjects who test positively will be dispensed

a [redacted] at-home dosing starting the following day and will return for Visit 3 [redacted]

At Visit 3 [redacted] subjects who continue to meet eligibility criteria and have consistent and sufficient ocular itching and redness [redacted] will be randomized into the study.

During the clinical trial period, subjects or caregivers will be instructed to instill one drop in each eye [redacted]

In addition to the [redacted], [redacted] be administered [redacted]

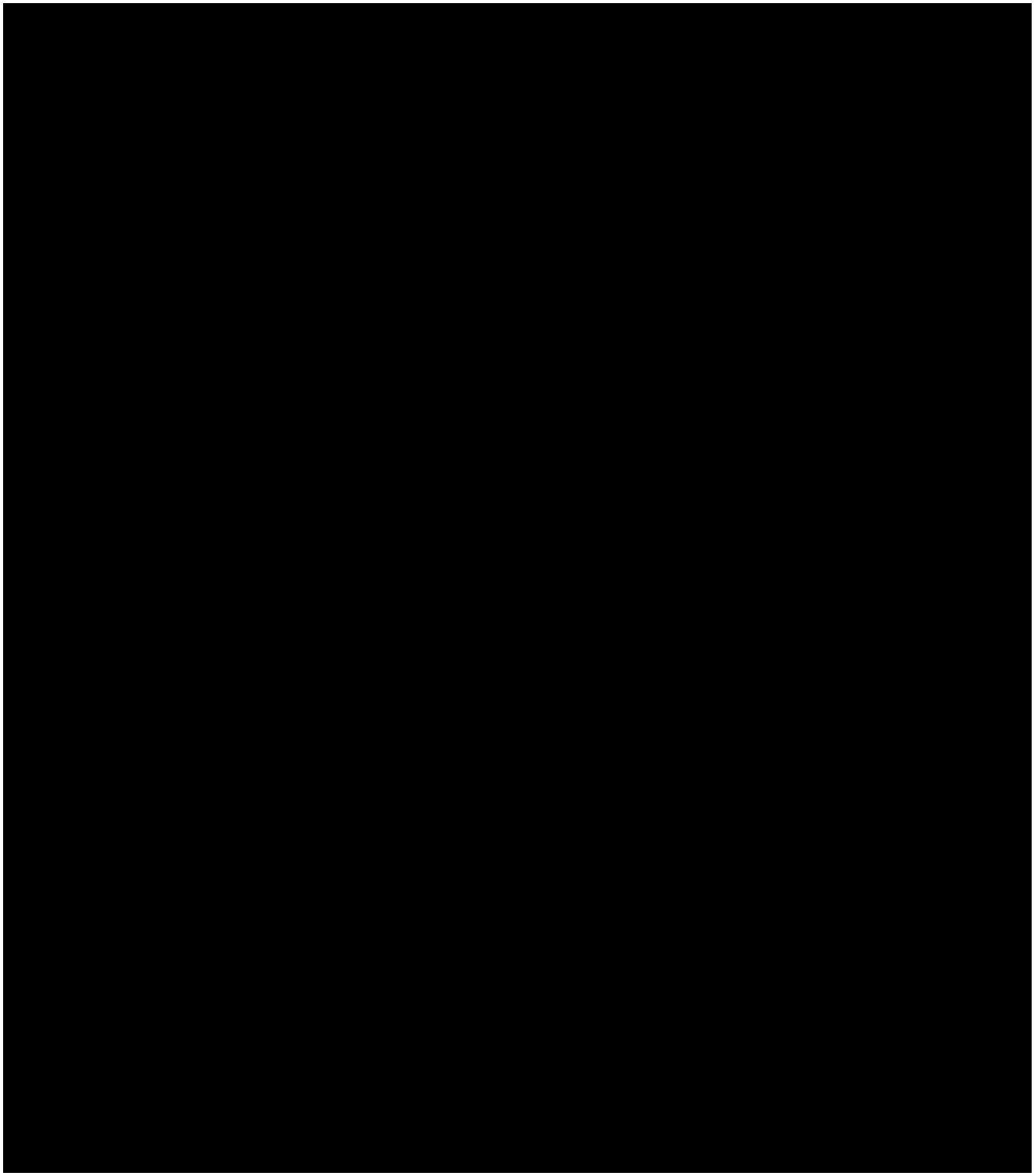
Subjects will return for a follow-up appointment at Visit 4 [redacted] where staff will collect, review, and dispense investigational product and review diaries. Subjects will return for an exit visit at Visit 5 [redacted].

Study visits will be referred to in all tables and listings as the visit and planned 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	Visit Window
Visit 1	Day -8	- 20 Days
Visit 2	Day -7	+ 3 Days
Visit 3	Day 1	NA
Visit 4	Day 15	±3
Visit 5	Day 29	+3

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.



5. Study Treatments

The study consists of three treatment arms:

- Reproxalap Ophthalmic Solution (0.25%);
- Reproxalap Ophthalmic Solution (0.5%);
- Vehicle Ophthalmic Solution.

5.1 Method of Assigning Subjects to Treatment Groups

All subjects screened for the clinical trial who sign an informed consent form will be assigned a three-digit screening number that will be entered in the Screening and Enrollment Log. Screening numbers will be assigned in a sequential order beginning with 001.

Each subject who meets all the inclusion and none of the exclusion criteria at Visit 3 [redacted] will be assigned the lowest 4-digit randomization number available at the given investigative site. Subjects will be randomly assigned to masked treatment [redacted]

5.2 Masking and Unmasking

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. The investigator should make every effort to contact the medical monitor at Ora, Inc. to discuss the subject's emergency situation and the need to unmask a clinical trial subject prior to unmasking the IP.

If the investigator determines that emergency unmasking is necessary, the investigator should identify the given subject's clinical trial drug 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 in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or serious AE (SAE) associated with breaking the mask must be recorded and reported as specified in the protocol. The investigator has the responsibility to contact Ora, Inc. within 24 hours of breaking the blind.

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

6. Sample Size and Power Considerations

Approximately [redacted] will be screened in order to enroll [redacted]

7. Data Preparation

All reported study data will be recorded on the electronic case report forms (eCRFs) supplied by Statistics and Data Corporation (SDC) [redacted] Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks, and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor and Ora in consultation with SDC.

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

- [redacted]

8. Analysis Populations

8.1 Intent-to-Treat

The Intent-to-Treat (ITT) population consists [redacted]

8.2 Per Protocol

The Per-Protocol (PP) population [redacted]

8.3 Safety

The Safety population includes [redacted].

9. General Statistical Considerations

9.1 Unit of Analysis

The subject will be considered the unit of analysis [redacted].

9.2 Missing or Inconclusive Data Handling

[redacted]

[redacted]

9.3 Definition of Baseline

In general, baseline is defined as the last observed measurement prior to the first dose of study medication; [redacted]

9.4 Data Analysis Conventions

All data analysis will be performed by SDC. Statistical programming and analyses will be performed using SAS®

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit.

9.5 Adjustments for Multiplicity

10. Disposition of Subjects

Subject disposition will be presented

.

Subject listings will be provided [redacted]

Protocol violations will be summarized [redacted] A subject listing will be provided [redacted]

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

The demographic variables collected [redacted]

A subject listing that includes all demographic variables will be provided.

11.2 Pretreatment Variables

At Screening, subjects signing the informed consent and Health Insurance Portability and Accountability Act (HIPAA) forms may be given a diagnostic test for allergic disease [redacted] Results [redacted] will be provided in a subject listing.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities [redacted]

[redacted]

Listings of medical history will be generated [redacted].

12.2 Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary [redacted]

[redacted] Listings of concomitant medications will be generated [redacted]

13. Dosing Compliance and Treatment Exposure

At Visit 3 [redacted] subjects will receive their first dose of IP in clinic and will be dispensed additional IP for at-home dosing. [redacted]

13.1 Treatment Exposure

Treatment exposure will be obtained [redacted]

[redacted]

IP instillation data for all subjects will also be provided in listings.

13.2 Dosing Compliance

Treatment compliance will be assessed [redacted]

[redacted]

Data pertaining to study drug assignment, instillation, accountability, etc., will be presented in subject listings.

14. Exploratory Efficacy Analyses

14.1 Subject Diary Data

Beginning after Visit 3 [redacted] and continuing to Visit 5 ([redacted] subjects are instructed to record allergic signs and symptoms [redacted]

[redacted]

14.1.1 Ocular Itching Subject Diary Scores

Ocular itching will be evaluated [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Figures will be created [redacted]

14.1.2 Ocular Itching Subject Diary Scores - Responders

The ocular itching diary data will also be analyzed [redacted]

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

[redacted]

[redacted]

14.1.3 Ocular Redness Subject Diary Scores

Ocular redness will be evaluated [redacted]

[redacted]

Figures will be created [redacted]

14.1.4 Eyelid Swelling and Tearing/Watery Eyes Subject Diary Scores

Eyelid swelling will be evaluated [redacted]

[redacted]

[redacted]

[redacted]

[redacted].

14.2 Scheduled Visit Ophthalmic Evaluations

The following assessments will be conducted [redacted]

- Ocular redness [redacted]
- Ocular itching [redacted]
- Ocular redness [redacted];
- Eyelid swelling [redacted];
- Tearing/watery eyes [redacted]

Each of these assessments will be analyzed [redacted]:

[redacted]

14.3 Allergic Conjunctivitis Quality of Life Questionnaire (ACQLQ)

The ACQLQ will be administered [redacted]

[redacted]

A subject listing of ACQLQ results will also be provided.

15. Safety Analyses

All safety analyses will be conducted [redacted]

15.1 Adverse Events

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. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. Additional details surrounding the definition of an AE, including SAEs, can be found in the study protocol. All AEs will be coded using MedDRA 21.0.

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

The relationship of each AE to the IP should be determined by the investigator using the following categories:

- Not related;
- Unlikely to be related;
- Possibly related;
- Probably related;

- Definitely related.

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 him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

- [redacted]

An overall summary will be presented that includes the number of AEs and the number and percentage of subjects who experienced at least one AE, by treatment group and for all subjects combined. This summary will also include breakdowns of AEs further categorized as ocular or non-ocular, SAEs, AEs by maximum severity and relationship to IP, number of subjects with AEs leading to treatment withdrawal and number of subjects with AEs resulting in death. TEAEs summarized for the same categories will also be included.

Additional summaries of AEs will be provided showing the number and percentage of subjects who experienced at least one AE. These summaries will be presented at the subject level by SOC and PT. 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 summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC. These summaries will be presented for ocular and non-ocular AEs separately and include the following:

- All AEs;
- All TEAEs;
- All TEAEs related to the IP (includes AEs possibly, probably or definitely related to IP);
- All SAEs; and
- All TEAEs by maximal severity.

Subject listings will be provided for all AEs, SAEs, AEs leading to death and AEs leading to study treatment discontinuation.

15.2 Visual Acuity

VA will be measured [redacted] Results for VA will be presented in a subject listing.

15.3 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination will be performed [redacted]

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

[redacted]

A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

15.4 Intraocular Pressure

IOP will be measured [redacted]

15.5 Dilated Fundoscopy Examination

Dilated fundus examinations will be performed [redacted]

16. Interim Analyses

No interim analysis is planned for this study.

17. Changes from Protocol-Stated Analyses

[redacted].

18. References

[1] Abelson, M. B., Chambers, W. A., & Smith, L. M. (1990). Conjunctival allergen challenge: a clinical approach to studying allergic conjunctivitis. *Archives of ophthalmology*, *108*(1), 84-88.

19. Revision History

[redacted]

[redacted]

20. Tables

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14.2.2.1.2	[redacted] Ocular Redness [redacted]	ITT Population with Multiple Imputations (MCMC)
14.2.2.1.3	[redacted] Ocular Redness [redacted]	PP Population with Observed Data Only
14.2.2.2.1	[redacted] Ocular Redness [redacted]	ITT Population with Observed Data Only
14.2.2.2.2	[redacted] Ocular Redness [redacted]	PP Population with Observed Data Only
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16.2.6.4	Eyelid Swelling [redacted]
16.2.6.5	Tearing [redacted]
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22. Figures

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14.2.2.1	[redacted] Ocular Redness [redacted]	ITT Population with Observed Data Only
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