[redacted]

STATISTICAL ANALYSIS PLAN

AN EXPLORATORY CLINICAL TRIAL EVALUATING REPROXALAP OPHTHALMIC SOLUTIONS (0.25% AND 0.5%) IN SUBJECTS WITH SEASONAL ALLERGIC CONJUNCTIVITIS USING THE ENVIRONMENTAL EXPOSURE CHAMBER (EEC)

Sponsor Protocol Number: ADX-102-AC-011
Final Version 4.0 Dated 22 NOV 2018

[redacted]

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03 March 2019
Final Version 1.0

[redacted]

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Sponsor Protocol No. ADX-102-AC-011

SAP Final Version Approvals

An Exploratory Clinical Trial Evaluating Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in Subjects with Seasonal Allergic Conjunctivitis Using the Environmental Exposure Chamber (EEC)

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations

AE	Adverse event
ADR	Adverse drug reaction
ANCOVA	Analysis of Covariance
AUC	Area under the curve
DBP	Diastolic Blood Pressure
EEC	Environmental Exposure Chamber
[redacted]	[redacted]
GINA	Global Initiative of Asthma
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IND	Investigational New Drug
IOP	Intraocular pressure
IP	Investigational product
IUD	Intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
NCT	Non-contact IOP tonometr
[redacted]	[redacted]
RR	Respiratory Rate
SBECD	Sulfobutylether-beta-cyclodextrin
SBP	Systolic Blood Pressure
SD	Standard deviation
SLE	Slit lamp examination
TOSS	Total ocular symptom score
VA	Visual acuity
WHO	World Health Organization

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I. INTRODUCTION

The purpose of the statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol 18-MO-001:

"An Exploratory Clinical Trial Evaluating Reproxalap Ophthalmic Solutions (0.25% And 0.5%) In Subjects With Seasonal Allergic Conjunctivitis Using The Environmental Exposure Chamber (EEC)"

This SAP is being written with due consideration of the recommendations outlined in the most recent International Council on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP is a summative and definitive plan, based on the final protocol dated November 22, 2018 (Version FINAL 4.0).

The SAP includes details of data handling procedures and statistical methodology. The SAP also outlines the statistical programming specifications for the Tables, Listings and Graphs (TLGs). No interim analysis is planned for this study.

The final statistical analysis will proceed exactly according to the SAP approved by the sponsor as well as by Inflamax Research.

The statistical analysis methods presented in this document will supersede the statistical analysis methods in the clinical protocol. If additional analyses are required to supplement the planned analyses described in the SAP, they will be labeled as post-hoc and will be identified in the CSR.

Responsibilities

Inflamax Research will perform the statistical analyses described herein and is responsible for the production and quality control (QC) of tables, figures, and listings associated with the analyses other than the post hoc analyses.

II. STUDY DESIGN

OVERVIEW OF STUDY DESIGN AND DOSING REGIMEN

ADX-102-AC-011/18-MO0001 is a single center study.

The double-masked, vehicle-controlled, randomized, three-way crossover clinical trial allows for

the testing of two concentrations of Reproxalap Ophthalmic Solution (0.25% and 0.5%) versus Vehicle Ophthalmic Solution in subjects with ragweed-induced allergic conjunctivitis in the EEC.

The clinical trial consists of five visits to the clinic (one Medical Screening visit, one Screening EEC visit, and three EEC treatment visits).The four EEC sessions (one EEC screening and three EEC treatment sessions) will be separated by an approximate two-week washout period to ensure adequate elimination of responses caused by allergen exposure in the EEC and allow the recuperation of mast cells, please refer to

Figure 1. Clinical Trial Design

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Subjects 18 years or older with allergic conjunctivis are eligible for this study. For the detailed inclusion and exclusion criteria, please defer to the current version of protocol.

Eligible subjects will be randomized 1:1:1 to one of three treatment sequences of ABC, BCA and CAB where:

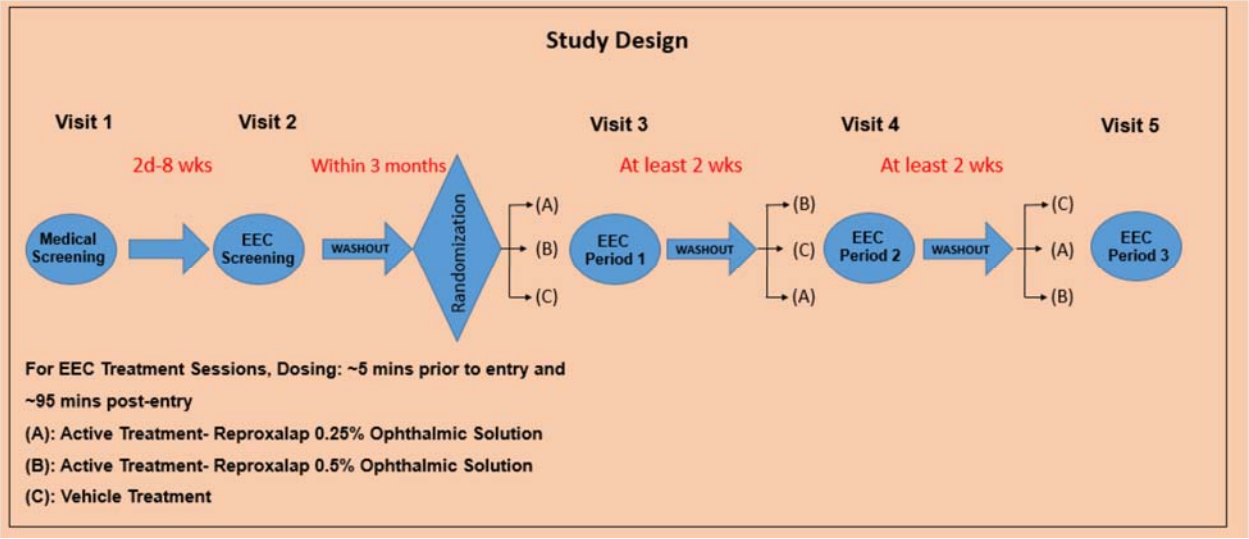
- Treatment A: Reproxalap Ophthalmic Solution (0.25%)
- Treatment B: Reproxalap Ophthalmic Solution (0.5%)
- Treatment C: Vehicle Ophthalmic Solution

Approximately 75 subjects (approximately 25 per treatment sequence) will be enrolled.

The clinical trial is exploratory in nature and the safety, tolerability, and pharmacodynamic activity of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) will be compared to Vehicle Ophthalmic Solution in subjects with allergic conjunctivitis in an EEC model. Pharmacodynamic endpoints for assessments of ocular itching, redness, and tearing will be evaluated. As an

exploratory study, there are no primary endpoints and no formal statistical hypotheses.

Figure 1. Clinical Trial Design



At the Medical Screening Visit (Visit 1), subjects will undergo the informed consent process, and information about demographics, baseline characteristics, medical history, social history, physical examination will be performed and concomitant medication will be collected. Vital signs and samples for standard clinical safety laboratory tests will be obtained. A urine pregnancy test will be administered to women of childbearing potential (WOCBP).

Subjects will undergo ophthalmic examinations (Snellen VA, SLE, NCT, and a dilated fundus examination) to ensure initial eligibility criteria are met. A skin prick test for a panel of test allergens will be conducted; results must be positive (i.e., a wheal that is 3 mm greater than the negative control) for at least one test allergen and must include ragweed in order to proceed to

Visit 2.

At all EEC sessions, assessments of ophthalmic evaluations will be collected [redacted] For subject-reported symptoms of ocular itching, a standard 9 point (i.e., 0-4 with 0.5 unit increments) and a standard VAS scale (0-100 mm) will be employed and subject reported tearing assessed by a 4-point (0-3) scale will be employed. For staff-assessed grading of conjunctival redness, a standard 9-point (i.e., 0-4 with 0.5 unit increments) will be employed. [redacted]

At the EEC Screening Visit (Visit 2), qualified site staff will update concomitant medications and collect AEs, as applicable and perform tests for vital signs. A urine pregnancy test will be administered to WOCBP. Fundus exam, Snellen VA, SLE, subject rating of symptoms, and staff grading of conjunctival redness will be performed to ensure the anterior segment of the eye is healthy. Designated site staff will administer saline solution in each eye just prior to EEC entry.

Pre-EEC entry (Baseline):

1) Subject assessment for ocular itching and tearing will be recorded [redacted] and
2) Staff-assessed conjunctival redness will be recorded [redacted].

Post-EEC entry:

1) Subject assessment for ocular itching and tearing will occur [redacted] 2) Staff-assessed conjunctival redness will be recorded [redacted]

Please refer to Table2, Table3, Table 4 and Table 5 for schedule of staff and subject assessment time-points.

[redacted]

At Randomization/Treatment EEC Session One (Visit 3), qualified site staff will update concomitant medications, collect AEs, as applicable and collect vital signs. A urine pregnancy test will be administered to WOCBP. Ophthalmic evaluations will be conducted (Fundus exam, Snellen VA, NCT SLE, subject rating of symptoms, and staff grading of conjunctival redness). [redacted]

Subjects will be randomized to receive a first dose of either Reproxalap Ophthalmic Solution (0.25%) (Treatment A), Reproxalap Ophthalmic Solution (0.5%) (Treatment B), or Vehicle Ophthalmic Solution (Treatment C). Qualified site staff will instill one drop of the randomized treatment into each eye at approximately five minutes prior to entry to the EEC after all the pre-EEC assessments are done.

Pre-EEC entry (Baseline):

1) Subject assessment for ocular itching and tearing will be recorded a[redacted] and
2) Staff-assessed conjunctival redness will be recorded [redacted].

Post-EEC entry:

1) Subject assessment for ocular itching and tearing will occur [redacted]
2) Staff-assessed conjunctival redness will be recorded [redacted].

At approximately 95-minutes post-EEC entry (and after subject assessed itching and tearing and staff assessed conjunctival redness for all time-points post first dose have been completed), a second dose (one drop in each eye) of the same randomized treatment will be administered in each eye by the qualified site staff. Subject will continue to assess symptoms of ocular itching and tearing after the second dose [redacted] and staff-assessed conjunctival redness will be recorded [redacted]

Post-EEC exit (approximately t=215 minutes):

1) Subject assessed ocular itching and tearing will continue [redacted];

2) Staff assessed conjunctival redness will continue to be recorded post-EEC exit [redacted].

Subjects will be asked to return in at least two weeks for Visit 4.

At Treatment EEC Session Two (Visit 4), all procedures performed at Visit 3 will be repeated except that each subject will be given a different treatment dependent on the treatment sequence the subject was randomized to [Reproxalap Ophthalmic Solution (0.25%) (Treatment A), Reproxalap Ophthalmic Solution (0.5%) (Treatment B), or Vehicle Ophthalmic Solution (Treatment C)].

At the end of the EEC session, subjects will be asked to return in at least two weeks (± 3 days) for Visit 5.

At Treatment EEC Session Three (Visit 5), all procedures performed at Visit 4 will be repeated except that each subject will be given a different treatment dependent on the treatment sequence the subject was randomized to [Reproxalap Ophthalmic Solution (0.25%) (Treatment A), Reproxalap Ophthalmic Solution (0.5%) (Treatment B), or Vehicle Ophthalmic Solution (Treatment C)]. At the end of the visit, a urine pregnancy test will be administered to WOCBP. Subjects will undergo ophthalmic examinations (Snellen VA, SLE, NCT, and a dilated fundus examination), clinical safety lab tests and vital signs will be collected to ensure safety prior to exit of the clinical trial.

Table1. Schedule of Events and Assessments

[redacted]

[redacted]

[redacted]	Sponsor: Aldeyra Therapeutics, Inc. Sponsor Protocol No. ALDNS2-203-D1

Table 2. Schedule of Staff-Assessed Conjunctival Redness Recording

[redacted]

Table 3. Schedule of Subject Assessed Itching and Tearing

[redacted]

Table 4. Schedule of Staff-Assessed Conjunctival Redness Recording Post-EEC Exit

[redacted]

Table 5. Schedule of Subject Assessed Itching and Tearing Post-EEC Exit

[redacted]

III. INVESTIGATIONAL TREATMENT

Reproxalap Ophthalmic Solutions (0.25% and 0.5%) and Vehicle Ophthalmic Solution are supplied as sealed Investigational Product (IP) kits, please refer to the current protocol for further.

IV. STUDY OBJECTIVES

- To evaluate the feasibility of using the EEC clinical trial design to assess the activity of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in an allergic conjunctivitis population.

- To assess safety, tolerability, and pharmacodynamic activity of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) compared to Vehicle Ophthalmic Solution in the treatment of seasonal allergic conjunctivitis in subjects allergic to ragweed using the EEC with exposure to airborne ragweed pollen.

V. DETERMINATION OF SAMPLE SIZE

[redacted]

VI. Randomization and Masking

Eligible subjects will be randomized 1:1:1 to one of three treatment sequences of ABC, BCA, CAB, where:

- Treatment A: Reproxalap Ophthalmic Solution (0.25%)
- Treatment B: Reproxalap Ophthalmic Solution (0.5%)
- Treatment C: Vehicle Ophthalmic Solution

Approximately 75 subjects (approximately 25 per treatment sequence) will be enrolled with a target of 60 completers. As the actual discontinuation rate observed was lower than anticipated, the enrollment may be less than the planned 75 subjects.

Investigators, qualified site personnel, and subjects will be masked to the treatment sequence and investigational product (IP) administered in each treatment visits. The Sponsor will also be masked to the IP administered information until database lock.

EMERGENCY UNBLINDING

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

The investigator should make every effort to contact the Medical Monitor to discuss the subject's emergency and the need to unmask, prior to unmasking any subject. Please defer to the protocol for further details.

SUBJECT NUMBERING

Each subject screened for the clinical trial will be assigned a unique subject number that will be used to identify the subject throughout their participation in the clinical trial. If a subject fails to be randomized, the reason should be documented in the source documents and case report form (CRF). The subject will be considered a screen failure.

VII. EFFICACY ASSESSMENTS

At all EEC sessions (pre- and post-entry), assessments of ophthalmic evaluations by subjects and qualified site staff will be collected using an electronic Patient Data Acquisition Tablet™ (ePDAT™).

Refer to **Table 2** (Schedule of Staff-Assessed Conjunctival Redness Recording) **Table 3** (Schedule of Subject Assessed Itching and Tearing Table 3for details on collection time points).

STAFF-ASSESSED SYMPTOM COLLECTION

At designated time points, qualified site staff will assess conjunctival redness in each subject using a standard 9-point (i.e., 0-4 scale with 0.5 unit increments).

[redacted]

[redacted]

[redacted]

SUBJECT ASSESSED SYMPTOMS

At designated time points, subjects will be asked to report and rate symptoms associated with allergic conjunctivitis, including ocular itching and tearing.

Ocular Itching

1. A Visual Analog Scale (VAS) measured on a 0- 100 mm continuous scale where 0 is considered no itching and 100 is considered maximum itch.

[redacted]

[redacted]

[redacted]

Ocular Tearing

[redacted]

[redacted]

[redacted]

VIII. SAFETY ASSESSMENTS

Safety assessments will include the following:

- Visual Acuity (VA) for Visit 1 through Visit 5.
- Slit Lamp Examination (SLE) for Visit 1 through Visit 5.
- Non-Contact intraocular pressure Tonometry (NCT) during Visit 1 and Visit 3 to Visit 5.
- Dilated Fundus Examination as Screening Visit 1 and Visit 5 and undilated Fundas examination at Visit 2, 3 and 4.
- Vital Signs (VS) for Visit 1 to Visit 5.
- Safety Clinical Laboratory parameters at Screening Visit 1 and at Visit 5.

- Adverse Events (AEs: reported, elicited and observed) from Visit 2 through Visit 5.

IX. ANALYSIS POPULATIONS

SAFETY POPULATION

All randomized subjects who received at least one dose of IP, regardless of whether clinical trial assessments were performed.

INTENT-TO-TREAT (ITT) POPULATION

All randomized subjects who received at least one dose of IP and have any post-dose assessments. Subjects are evaluated according to the IP treatment of the visit as per the randomized treatment sequence.

COMPLETER POPULATION

COMPLETER population will include all randomized subjects who received IP dosing at all three EEC treatment visit.

PER-PROTOCOL (PP) POPULATION

All ITT subjects will be considered PP if IP dosing occurs and do not have a major deviation from the protocol. The following is a list of protocol violations which would exclude subjects from the PP population:

- Subject did not receive IP as assigned.
- Subject did not meet all inclusion/exclusion criteria.

X. ENDPOINTS

EFFICACY ENDPOINTS

The following efficacy endpoints will be derived for each pharmacodynamic measures in each treatment visit and will be used to assess the activity of Reproxalap Ophthalmic Solutions.

- AUC 0-212 mins for Itching on VAS scale
- AUC 0-212 mins for Itching on 9 points scale
- AUC 0-210 mins for Conjunctival Redness on 9 points scale
- AUC 0-212 mins for Tearing on 4 points scale
- AUC 0-212 mins for TOSS
- AUC 0-92 mins for Itching on VAS scale

- AUC 92-212 mins for Itching on VAS scale
- AUC 0-32 mins for Itching assessed by VAS Scale
- AUC 32-92 mins for Itching assessed by VAS Scale
- AUC 0-274 mins for Itching on VAS scale
- AUC 0-274 mins for Itching on 9 points scale
- AUC 0-270 mins for Conjunctival Redness on 9 points scale
- AUC 0-274 mins for TOSS

Since there are time windows available for symptom assessments, all time points above refers to the planned nominal time points and the actual elapsed time points may differ from the nominal time points. For detailed derivations of these parameters, please see SAP Appendix 1, Calculations.

SAFETY ENDPOINTS

- Adverse Events/Adverse Drug Reactions
- Intraocular Pressure Readings (IOP)
- Visual Acuity (VA)

XI. STATISTICAL METHODOLOGY

Summary Statistics

Unless the list of summary statistics is specified for any summary table, the standard summary statistics that will be calculated for quantitative and qualitative variables are:

Quantitative:	sample size (number of subjects), mean, median, standard deviation, minimum and maximum of the raw data
Qualitative:	sample size (number of subjects), absolute and relative frequencies per class

The summarization will be done by three treatment groups and at every scheduled time point (if applicable) for every endpoint.

Reporting Precision

Summary statistics will be presented to the following degree of precision:

Statistics	Degree of precision
Mean (of all kinds), Median, Quartiles, Confidence Intervals	one more than the raw data
Standard deviation, Standard error	two more than the raw data
Minimum, Maximum	the same as the raw data
P-value	rounded to 3 decimal places and therefore presented as 0.xxx; P-values smaller than 0.001 as '<.001'
Percentage, Coefficient of variation	one decimal place

Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 - 0.30, not .12 - .30).

Common Definitions and Labels

Study Day is the number of days since administration of study drug during a Treatment Period, which is counted as Study Day 1. Study Day is derived separately for each of the 3 treatments.

Nominal Time is the scheduled measurement time relative to the dose time.

Study Time or Actual Elapsed Time is the time from the last administration of study drug. So, for example, if study drug is administered at 08:00 on Day 1, 10:00 on Day 1 represents a study time (or actual elapsed time) of 2:00 hours.

Data Collected Outside Study Schedule

Data collected at visits that occurred outside the time windows specified in the protocol will be included in the data listings but will not be included in the analyses.

Definition of Baseline

In general, baseline is defined as the last observed measurement prior to the first dose of study medication during Pre-EEC entry at visit (visit 3, visit 4 and visit 5). If patient has more than one non-missing measurement at different time point prior to the first dose, average of these assessment score will be taken to derive the baseline value. The baseline will be used in the change from baseline calculation for each treatment period.

Derived Variables

- Age is calculated in years after rounding down as follows:
  Year of age = (Date [in days format] informed consent signed - Date [in days format] of birth) / 365.25.

- Efficacy assessments will be performed on both eyes. For conjunctival redness, assessments will be made in both temporal and nasal regions. For a symptom and at a specific EEC time point, from the multiple scores observed, the maximum score from both eyes and regions when applicable will represent the worst symptom score and thus will be used for the statistical analysis. This implies that all efficacy summary tables and treatments comparisons will use the maximum observed score at each ECC time points. The Listings of efficacy data however will provide all scores for the eyes and the regions as applicable.

  The efficacy endpoints AUC will also be derived using the maximum score at each time point. Similarly, TOSS will be derived using the maximum score at each time point for the ocular itching, conjunctival redness and tearing symptoms.

- TOSS will be derived as the sum total of maximum score from ocular itching, conjunctival redness and tearing symptoms. However, the EEC time points for the ocular itching and tearing symptoms is different from the time points for the conjunctival redness. The scheduled time points for ocular itching will be used to represent the TOSS scheduled time points.

XII. STATISTICAL ANALYSES

MISSING DATA

Any missing values for the efficacy endpoints for a subject during a visit and a specific time point will be imputed and replaced by the mean value calculated from all non-missing values of the same symptom for the same visit and the time point from all other subjects who has taken the same treatment in that visit.

The imputed missing value for conjuctival redness and itchiness symptoms will be rounded to the nearest 0.5 value in order to match the observed scales. The imputed missing value for tearing symptom will be rounded to the nearest integer value in order to match the observed scale.

ADJUSTMENTS FOR MULTIPLICITY

No multiplicity adjustments will be conducted in this study.

INTERIM ANALYSIS

No interim analysis is planned for this study.

GENERAL CONSIDERATIONS

[redacted]

SUBJECT POPULATIONS AND DISPOSITION

The listing of randomization scheme will be presented with subject identification, sex, age, race, and assignments to the treatment sequence. The following frequencies (number and percent) will be displayed by treatment group and for all subjects combined:

- Subjects Randomized
- Subjects who completed all treatment sessions
- Subjects in the Safety Population
- Subjects in the ITT Population
- Subjects in the COMPLETER Population
- Subjects in the PP Population
- Subjects who withdrew early (total and by reason)

The denominators for the percent calculations will be the number of subjects randomized, whether or not they are included in any of the analyses.

DISCONTINUATIONS

In the event that any subject is withdrawn or withdraws from the study, a table presenting all subjects withdrawn will be provided. The listing will include subject identifier, visit at withdrawal, time point, treatment ID, and last treatment received prior to withdrawal and the specific reason(s) for withdraw. If a sufficient number of subject withdrawal happens, the frequencies (number and percent) of discontinuations by reason will be presented by last treatment administered and for all subjects combined.

PROTOCOL DEVIATIONS/VIOLATIONS

All deviations including but not limited to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment will be listed.

If numbers are sufficient, protocol deviations will be summarized (number and percent of subjects) by type of deviation. The protocol deviations will be grouped into different categories which may include, but are not limited to:

- Missed visit
- Inclusion/Exclusion criteria
- Missed procedures/assessments
- Informed consent
- Documentation
- Study drug administration
- Safety
- Lack of compliance

DATA SETS ANALYZED

A listing of subjects excluded from the Safety, ITT, COMPLETER and PP populations will be produced.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and baseline characteristics will be listed by subject and summarized by Analysis Populations using standard summary statistics.

- Gender, Ethnicity and Race

- Age (years), height (cm), weight (kg) and BMI (kg/m2)
- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)
- Heart rate (beats/minute)
- Pulse rate (beats/min)
- Respiratory rate (breaths/minute)
- Medical History
- Skin Prick Test

Unless stated otherwise, percentages will be calculated out of the number of patients in the given Analysis Set.

PRE-EEC MEASUREMENT FOR VISIT 3, 4 AND 5

Summary statistics of following pre-EEC measurement at Visit 3 to Visit 5 will be tabulated by treatment, visit and eye.

- Fundus exam
- Snellen VA
- NCT
- SLE
- Subject rating of ocular itching and tearing
- Staff grading of conjunctival redness

MEDICAL HISTORY AND CONCOMITANT DISEASES.

Description of medical history and concomitant disease findings prior to screening will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher. Medications will be coded according to the WHO drug dictionary which includes the WHO Drug Preferred Name and the ATC Classification Level 2 and 4. Prior and concomitant medication data will be listed by subject.

A disease or illness reported at Screening reported as medical history without a start date will be included in medical history without a date assigned. Medical history will be sorted by descending overall frequency, by SOC and PT in the summary table. Medical history data listings will be sorted by treatment, patient number, start date, SOC and PT.

CONCOMITANT MEDICATION

Concomitant medication, prescription or over-the-counter will be defined as, taken within 30 days prior to Visit 1 through to Visit 5, is to be recorded on the source document and

corresponding electronic CRF along with the reason the medication was taken.

Medications will be coded according to the WHO drug dictionary which includes the WHO Drug Preferred Name and the ATC Classification Level 2 and 4. Prior and concomitant medication data will be listed by subject.

STUDY DRUG ADMINISTRATION

The dosing dates, times during Treatment Visits 3 to 5 will be listed by subject and visit.

EFFICACY ANALYSES

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Treatment Comparisons

[redacted]

[redacted]

The following 3 contrasts will be evaluated for each primary endpoint:

- Reproxalap Ophthalmic Solution (0.50%) vs. Placebo
- Reproxalap Ophthalmic Solution (0.25%) vs. Placebo
- Reproxalap Ophthalmic Solution (0.50%) vs. Reproxalap Ophthalmic Solution (0.25%)

[redacted]

POST HOC ANALYSIS

1. Additional inferential analysis may be performed whereby additional covariates and other fixed factors may be used in models, depending on the significance of the term and the impact on contrast outcomes.
2. Responder analyses may be performed whereby treatment response may be defined as one and two-point improvements from mean and within-subject baseline and peak scores. In addition to GEE, time to event analyses may also be performed.

[redacted]

[redacted]

SAFETY ANALYSES

All safety data will be analyzed using Safety population.

For safety analysis, summary descriptive statistics such as N, mean, SD, median, minimum and maximum will be provided by treatment group for continuous variables. Frequency distribution as number of subjects and percentage of subjects will be provided for categorical variables. No formal inferential tests will be performed on safety data.

Adverse Events/Adverse Drug Reactions

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary [redacted] preferred term (PT) and system organ classification (SOC). Subjects will multiple events within the same SOC and/or PT are only counted once within the respective frequencies.
An AE will be considered treatment emergent (TEAE) if it begins or worsens in severity after the first dose of the double-blind Study Treatment through 28 days after the last dose of Study Treatment, or the date of initiation of another investigational agent or surgical intervention
Each AE is to be evaluated for date/time of onset, duration, ocular versus non-ocular, severity, outcome and causal relationship with the study drug or other factors.

Derived and Imputed Data

TEAEs will be assigned to a treatment based on the time of occurrence in relation to the last treatment administered prior to the onset of the TEAE. Time since last dose at time of onset will be calculated as the difference between the onset date and time and the date and time of the last dose of the treatment at onset. Time since last dose will be expressed in days, hours and minutes. Duration will be calculated for AEs that resolve as the difference between the resolution date and time and onset date and time. Duration will be expressed in days, hours and minutes.

Based on the MedDRA preferred term, subjects who experience the same AE on multiple occasions will be summarized at the maximum severity and most conservative relationship to the study medication. If 2 or more AEs are reported as a single event, the individual terms will be reported as separate AEs.

Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as a "serious Adverse Event (Y)" on the adverse events page of the CRF. A summary of serious TEAEs and Serious treatment related TEAEs by SOC and PT will be prepared.

Adverse Events Leading To Death

Adverse events leading to death are those events with 'Death' recorded under Outcome in the adverse events page of the CRF. A summary of TEAEs and SAEs leading to death by SOC and PT will be prepared. A listing of AEs leading to death will be included with the TEAEs flagged.

Data Summarization

TEAEs will be classified and summarized according to the treatment at onset of the AE. The summary of TEAEs after the study drug administration on Visit 3 of Treatment Period 1 will be presented grouped by three treatments.

The AEs will be summarized by MedDRA system organ class and preferred term for each treatment group.

Treatment-emergent AEs (TEAEs) will be tabulated separately for safety population overall, and for ocular/non-ocular, by treatment group:

- Summary of TEAEs categorized by death, serious AEs, leading to withdrawal and related to study drug (safety/ocular/non-ocular)
- Summary of TEAEs by system organ class and MedDRA preferred term (safety/ ocular/non-ocular)
- Summary of TEAEs by severity (safety)
- Summary of TEAEs by relation to study drug (safety)

Adverse events will be listed as:

- Adverse events by subject and AE number
- Adverse events that caused the subject to discontinue
- Serious AEs

Severity.

Severity is classified as mild, moderate or severe. Missing severity for TEAEs will be counted as severe.

Adverse events with a missing relationship to study medication will be noted as "related" to study medication. If a patient reports the same AE more than once within the same SOC/PT, the AE with the strongest relationship to study medication will be used in the relationship summaries.

Pregnancies

Urine pregnancy tests will be performed from Screening Visit 1 through final treatment Visit 5. Pregnancy test results will be listed by subject and visit.

Vital signs

Blood pressure (systolic and diastolic, mm Hg), pulse rate (beats/min), respiratory rate (breaths/min) and body temperature (degree Celsius) will be assessed from Screening Visit 1 to final treatment Visit 5. The vital signs at EEC Visit 5 will be assessed at pre and post EEC time points, whereas the vital signs at EEC Visit 3 and Visit 4 will only be made at pre EEC time point. All vital signs data will be listed by subject, visit and time point as applicable.

Fundus Assessment

Fundus assessment will be performed at Screening Visit 1 to final treatment Visit 5, and will be listed by subject, visit and eye.

Intraocular Pressure Readings (IOP)

Non-contact tonometry (NCT) assessment will be performed at Screening Visit 1 and at Visit 3 to Visit 5 to measure the Intraocular Pressure (IOP). The collected data (average of 3 readings for each eye) will be listed by subject, treatment, visit and time point as applicable. Summary statistics of the average of 3 IOP readings for treatment Visit 3 to Visit 5 for each eye will be tabulated by treatments and time points and presented for both Right and Left eyes.

Visual Acuity (VA)

VA assessment will be performed at each visit. Data will be listed by subject, visit, treatment, time point and eye as applicable. Summary statistics of Visual Acuity for treatment Visit 3 to Visit 5 will be tabulated by treatment and eye.

Slit lamp Assessment

Slit lamp assessment will be performed at each visit. Data will be listed by subject, visit, treatment, time point and eye as applicable. Abnormalities and clinically significant findings will also be listed.

CHANGE TO THE PLANNED ANALYSES

The final version of the protocol specified additional efficacy assessments for Post-EEC exit time points. However, the list of efficacy endpoints in the protocol do not cover the data related to these Post-EEC exit time points. Therefore, the following additional efficacy endpoints were added in the SAP.

- AUC 0-274 mins for Itching on VAS scale
- AUC 0-274 mins for Itching on 9 points scale
- AUC 0-270 mins for Conjunctival Redness on 9 points scale
- AUC 0-274 mins for TOSS

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	

TABLES, LISTINGS AND FIGURES (TLFS)

The TLFs shells for this study is provided in a separate document SAP Mock TLFs. The shells may change due to unforeseen circumstances such as data formatting. These shells may not be reflective of every aspect of this study but are intended to show the general layout of the Tables, Listings and Figures that will be included in the final report. TLFs are numbered following the E3 "Structure and Content of Clinical Study Report".

[redacted]