Clinical Trial Protocol: ADX-102-DED-021

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Clinical Trial Evaluating the Safety of 0.25% Reproxalap Ophthalmic Solution in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-021
Study Phase:	3
Product Name:	0.25% Reproxalap Ophthalmic Solution
[redacted]	
Indication:	Dry Eye Disease (DED)
Investigators:	Multi-Center
Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Ave. Lexington, MA 02421 USA
Contract Research Organization:	[redacted]
IRB:	[redacted]

[redacted]

Confidentiality Statement

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SPONSOR PERSONNEL

[redacted]

ORA PERSONNEL

[redacted]

SYNOPSIS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Clinical Trial Evaluating the Safety of 0.25% Reproxalap Ophthalmic Solution in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-021
Study Drug:	1) 0.25% Reproxalap Ophthalmic Solution (reproxalap) 2) Vehicle Ophthalmic Solution (vehicle)
Study Phase:	3
Study Objective:	To compare the safety of reproxalap to vehicle in patients with dry eye disease
Overall Study Design	
Structure:	Multi-center, double-masked, randomized trial
Duration:	An individual subject's participation is estimated to be approximately 6 weeks (42 days) or 1 year (360 days).
Control:	Vehicle Ophthalmic Solution (vehicle)
Dosage/Dose Regimen:	Subjects will qualify for enrollment at Visit 1 and will be randomized to one of the following treatments: •Treatment A: 0.25% Reproxalap Ophthalmic Solution •Treatment B: Vehicle Ophthalmic Solution Subjects who are in the trial for 6 weeks will dose four times daily (QID) with reproxalap or vehicle for the first 4 weeks and two times daily (BID) for the remaining two weeks. Subjects who are in the trial for 1 year (LTFU) will dose QID with reproxalap or vehicle for the first 4 weeks and BID for the remaining 11 months.
Summary of Visit Schedule:	3 visits over the course of approximately 6 weeks OR 7 visits over the course of 1 year (LTFU Cohort)

	• Visit 1 = Screening & Randomization • Visit 2 = Day 29 ± 3, 4-Week Follow-Up • Visit 3 = Day 43 ± 4, 6-Week Follow-Up (Exit for approximately 300 subjects) • Visit 4 = Day 90 ± 7, 3-Month follow-up • Visit 5 = Day 180 ± 7, 6-Month follow-up • Visit 6 = Day 270 ± 10, 9-Month follow-up • Visit 7 = Day 360 ± 10, 1-Year follow-up & Exit
Measures Taken to Reduce Bias:	Randomized treatment assignment, double-masked trial
Study Population Characteristics	
Number of Subjects:	Approximately 1050 subjects are expected to be screened to enroll 850 subjects into the trial. Approximately 550 subjects will continue after Week 6 for the Long-Term Follow-up portion, with the goal of approximately at least 100 reproxalap subjects completing at 1 year.
Condition/Disease:	Dry Eye Disease (DED)

Inclusion Criteria:	**Subjects must meet all of the following criteria:** 1. At least 18 years of age (either gender and any race); 2. Ability to provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form; 3. Reported history of dry eye for at least 6 months prior to Visit 1; 4. History of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; [redacted]
Exclusion Criteria:	**Subjects must not meet any of the following criteria:** 1. Clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation, or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters; 2. Diagnosis of an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1; 3. Contact lens use within 7 days of Visit 1 or anticipate using contact lenses during the trial; 4. Eye drop use within 2 hours of Visit 1;

	5. Previous laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months; [redacted] 7. Planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1; 8. Temporary punctal plugs during the study that have not been stable within 30 days of Visit 1; 9. Use of and unwillingness to discontinue topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs for the duration of the trial (excluding medications allowed for the conduct of the trial); [redacted] 11. Pregnancy, nursing, or planned pregnancy during the conduct of the trial; 12. Unwillingness to submit a urine pregnancy test at Visit 1 and Visit 43 (6-week subjects)/Visit 7 (LTFU subjects) (or early termination visit) if of childbearing potential. (Non-childbearing potential is defined as a woman who is permanently sterilized [e.g., has had a hysterectomy or tubal ligation], or is post-menopausal [without menses for 12 consecutive months]; 13. If of childbearing potential, unwillingness to use an acceptable means of birth control.

	(Acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device [IUD]; or surgical sterilization of partner. For non-sexually active males or females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, he/she must agree to use adequate birth control as defined above for the remainder of the trial.); 14. Known allergy and/or sensitivity to the test article or its components; 15. A condition or be in a situation which the investigator interprets may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study; 16. Abnormal endothelial cell count (LTFU subjects only); 17. Current enrollment in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; 18. Previous reproxalap use within the past year; 19. Inability or unwillingness to follow instructions, including participation in all study assessments and visits.
Study Formulations and Formulation Numbers:	0.25% Reproxalap Ophthalmic Solution Vehicle Ophthalmic Solution
Evaluation Criteria	
Primary Safety Endpoints	• Proportion of subjects that experience at least one treatment-emergent severe adverse event (TE-SAE) of a visual

	acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to Investigational Product (IP) • Proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP • Proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP • Proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP
Safety Evaluation Criteria:	• Visual acuity • Slit-lamp evaluation • Adverse event query • Intraocular Pressure (IOP) • Dilated fundoscopy • Central Cornea Endothelial Cell Counts (1-year LTFU subjects) • Blood chemistry and hematology analysis in a subset of subjects (1-year LTFU subjects only) • Unanesthetized Schirmer's Test [redacted]
Other Measures:	• Urine Pregnancy Test
General Statistical Methods and Types of Analyses Analysis Populations • Safety Population – The Safety population will include all subjects receiving treatment from whom at least one safety measurement is obtained following the first dose of study drug. The Safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.	

- Safety-LTFU Population – The Safety population will include all LTFU subjects receiving treatment from whom at least one safety measurement is obtained following the first dose of study drug. The Safety-LTFU population will be analyzed for all safety assessments. Subjects in the Safety-LTFU population will be analyzed as treated.

Sample Size

[redacted]

[redacted]

Table 1: Assumed True Event Proportions

[redacted]

[redacted]

[redacted]

[redacted]

Table 2: Assumed True Event Proportions

[redacted]

Multiplicity

All primary safety endpoints will be tested with an overall study-wide two-sided alpha level of 0.05 with the primary safety endpoints evaluated using the Safety population with 6 weeks of follow-up being tested at a two-sided alpha level of 0.0165 and the primary safety endpoints using the Safety-LTFU population with 6 months (and 1-year) of follow-up being tested at a two-sided alpha level of 0.0335.

For the primary safety endpoints using the Safety population with 6 weeks of follow-up, Bonferroni correction will be used to account for multiple endpoint testing. For example, each primary safety endpoint tested using the Safety population with 6 weeks of follow-up will be assessed at the two-sided alpha level of 0.004125. For the interim analyses, no type I error adjustment will be made as 100% of the information will be available for the primary endpoints using the Safety population with 6-weeks of follow-up.

[redacted]

Primary Safety Analyses

The following endpoints will be formally tested in both the Safety and Safety-LTFU populations at interim and final analysis [redacted]

- Proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP
- Proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP
- Proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP
- Proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP

The primary safety comparisons in this trial will be between 0.25% Reproxalap versus Vehicle in the Safety Population using the following primary estimand:

Estimand 1

- Populations:
  - Subjects with DED defined through enrollment criteria that are enrolled in either the 6-week follow-up or 1-year follow-up schedule.
  - Subjects with DED defined through enrollment criteria that are enrolled in the 1-year follow-up schedule only.
- Endpoints:

  Safety population at 6 weeks:

  Proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP within 6 weeks of study drug dosing in the Safety

populationProportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of ≥ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP within 6 weeks of study drug dosing in the Safety population

- Proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP within 6 weeks of study drug dosing in the Safety population
- Proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP within 6 weeks of study drug dosing in the Safety population

Safety-LTFU population within 6 months (or 1 year):

- Proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP within 6 months/1 year of study drug dosing in the Safety-LTFU population
  Proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of ≥ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP within 6 months/1 year of study drug dosing in the Safety-LTFU population
- Proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP within 6 months/1 year of study drug dosing in the Safety-LTFU population
- Proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP within 6 months/1 year of study drug dosing in the Safety-LTFU population

- Intercurrent event:
  - Discontinuation of study medications is ignored, measures obtained after discontinuation of study medication will be analyzed. [treatment policy strategy]
  - Non-optimal compliance is ignored, measures will be analyzed regardless of treatment compliance. [treatment policy strategy]
  - Use of prohibited alternative therapies is ignored, measures obtained after initiation of prohibited therapies will be analyzed. [treatment policy strategy]
  - Discontinuation of study, subjects that discontinue study prior to time point of interest for an endpoint (Ex. 6 weeks or 6

months/1 year) AND do not experience event of interest will not be analyzed. [principal stratum strategy]
    - Discontinuation of study, values post-discontinuation will not be imputed. [while on treatment strategy]
- Population-level summaries:
    - Difference in the proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP
    - Difference in the proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP
    - Difference in the proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP
    - Difference in the proportion of subjects with at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP

Frequencies and percentages of subjects from each treatment group will be reported. Differences in proportions for each endpoint will also be reported.

[redacted]

Sensitivity analyses of the primary safety endpoints may include repeating primary analyses with alternative handling of intercurrent events with different estimands. In addition, sensitivity analyses using incidence rates (events/person-time) will be produced. Details will be outlined in the Statistical Analysis Plan (SAP), which will dominate any statistical language herein.

Other Safety Analyses

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature treatment discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term for the following categories of AEs:

- All TEAEs
- TEAEs at least possibly related to study treatment
- TEAEs leading to study treatment discontinuation
- Serious TEAEs (SAEs)

- By maximal severity
- By study day of onset

Separate analyses will be performed for ocular and non-ocular AEs. Further analyses of AEs will be specified in the SAP.

Other safety endpoints will be summarized by treatment group and visit using descriptive statistics using the Safety population or Safety-LTFU population. Changes or shifts from baseline will also be summarized where appropriate. Assessments performed by eye will be summarized separately for right eye (OD) and left eye (OS).

For quantitative safety endpoints, comparisons between treatment groups will be made at the eye level. [redacted]

Summary of Known and Potential Risks and Benefits to Human Subjects

There are no known safety risks of topical ocular reproxalap, which has been administered to 968 subjects across 8 Phase 2 and Phase 3 clinical trials in concentrations of 0.1%, 0.25%, and 0.5%, up to 4-times-daily for 12 weeks and 8-times-daily tapered to 4-times-daily over 4 weeks in healthy volunteers and in subjects with dry eye disease, allergic conjunctivitis, and noninfectious anterior uveitis. No consistent changes in visual acuity, slit-lamp evaluation, IOP, dilated fundoscopy, or non-ocular adverse events have been observed. No treatment-related serious adverse events have been observed. [redacted]

Reproxalap has demonstrated consistent, statistically significant, and clinically meaningful activity in dry eye disease, allergic conjunctivitis, and noninfectious anterior uveitis as assessed by change from baseline and improvement over vehicle.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
BID	twice daily
[redacted]	
CRO	Contract Research Organization
DED	Dry Eye Disease
DHHS	Department of Health and Human Services
eCRF	electronic case report form
EKG	electrocardiograph
ERC	ethical review committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IND	investigational new drug application
IP	investigational product
IOP	intraocular pressure
IRB	institutional/independent review board
IUD	intra uterine device
IWRS	Interactive Web Response System
LASIK	laser *in situ* keratomileusis
logMAR	logarithm of the minimum angle of resolution
LPS	lipopolysaccharide
LTFU	Long-Term Follow-up
MDA	malonyldialdehyde
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
mm	millimeter
µL	microliter
mmHg	millimeters of mercury
OD	right eye
OS	left eye
OTC	over-the-counter
QID	four times daily
RASP	reactive aldehyde species
SAE	serious adverse event
TEAEs	treatment emergent adverse events
TMF	Trial Master File
VA	visual acuity
WHO	World Health Organization

1 INTRODUCTION

Dry eye disease (DED) is a complex and chronic condition characterized by ocular discomfort, visual disturbance, tear film instability, increased tear osmolarity, and inflammation of the ocular surface that, in severe cases, can lead to loss of vision (Dry Eye Workshop 2007). Although estimates of the prevalence of dry eye disease vary considerably depending on the criteria used to define the disease, as many as 3.2 million women and 1.7 million men over the age of 50 are thought to have DED in the United States, and prevalence is projected to increase by 40% by 2030 as a result of population aging and increasing computer use (Schaumberg 2002, Schaumberg 2003, Schaumberg 2009, Brewitt 2001).

Reactive aldehyde species (RASP) are reactive organic molecules that bind to proteins, carbohydrates, lipids, and nucleic acids (Esterbauer 1991). RASP that are not sequestered or otherwise protected in specific metabolic processes are toxic, and aldehyde binding to cellular constituents leads to inflammation via activation of NFκB and other pro-inflammatory mediators (Yadav 2013), molecular dysfunction (O'Brien 2005), and the accumulation of indigestible metabolites, such as lipofuscin components in the retina (Boyer 2012).

In biological systems, RASP are formed by a variety of processes, including the oxidation of alcohols, polyamine and glucose metabolism, and oxidative stress. In non-disease states, levels of RASP are low due to the near ubiquitous presence of aldehyde dehydrogenases and other enzymes that catabolize aldehydes. However, in disease states, the capacity of aldehyde dehydrogenases to neutralize toxic aldehydes is exceeded, resulting in increased RASP levels. Elevation in the levels of RASP, particularly malonyldialdehyde (MDA), has been described in a variety of inflammatory ocular diseases, including pterygium, Behcet's Disease, Sjögren's Syndrome, anterior uveitis, and dry eye disease (Sandikci 2003, Cejkova 2007, Balci 2011, Turk 2014, Choi 2016, Augustin 1995).

Reproxalap is a novel small molecule, formulated for topical ophthalmic delivery that functions as a RASP sequestering agent, or "trap," which binds rapidly and irreversibly to RASP. By irreversibly trapping RASP, reproxalap is expected to diminish inflammation thought to be caused or exacerbated by elevated RASP levels in inflammatory ocular conditions. Reproxalap has demonstrated anti-inflammatory effects in numerous ocular and non-ocular preclinical models of inflammation:

- In a rat model of lipopolysaccharide (LPS)-induced uveitis, topical ocular dosing of reproxalap significantly reduced inflammatory ocular effects and significantly reduced ocular levels of two pro-inflammatory cytokines.
- In a rabbit ocular healing study, topical ocular reproxalap significantly reduced haze intensity and reduced the rate of haze development following photorefractive keratectomy.
- In a model of LPS-induced systemic inflammation, a single intraperitoneal dose of reproxalap led to a significant reduction in levels of several pro-inflammatory cytokines, while also increasing levels of the anti-inflammatory cytokine IL-10.

- In a phorbol 12-myristate-13-acetate-induced mouse model of contact dermatitis, intraperitoneal administration of reproxalap significantly reduced edema.
- In an oxazolone-induced, delayed-type hypersensitivity mouse model, intraperitoneal administration of reproxalap significantly reduced edema and resulted in statistically significant reduction of tissue cytokines at the site of inflammation.
- In a mouse model of lung inflammation, intraperitoneal administration of reproxalap reduced infiltration of inflammatory cells and protein in the lung, and resulted in reductions in levels of pro-inflammatory cytokines.
- In a model of radiation-induced mucositis in hamsters, subcutaneous administration of reproxalap significantly improved healing time and reduced fibrosis (scarring).

In 1995, Augustin et al. (Augustin 1995) described elevations in tear MDA levels that correlated with severity in DED patients. Subsequently, Choi et al. (Choi 2016) reported that expression of MDA and 4-hydroxynonenal (another RASP commonly associated with inflammation) is increased in the tear film and ocular surface of patients with DED. Consistent with the literature that supports the notion that RASP mediate pro-inflammatory toxicity in DED, the anti-inflammatory effects of the RASP scavenger reproxalap have been demonstrated in Phase 2 clinical trials in DED, noninfectious anterior uveitis (Mandell 2020), and allergic conjunctivitis. In aggregate, a broad array of preclinical and clinical evidence supports the use of reproxalap for the treatment of ocular inflammation, including DED.

2 STUDY OBJECTIVES

The objective of this study is to compare the safety of topical ocular 0.25% reproxalap to vehicle in patients with dry eye disease.

3 CLINICAL HYPOTHESES

N/A

4 OVERALL STUDY DESIGN

The ADX-102-DED-021 clinical trial is a Phase 3, multicenter, randomized, double–masked, parallel-group, vehicle-controlled design. Subjects will be randomized to one of the following treatment groups at Visit 2:

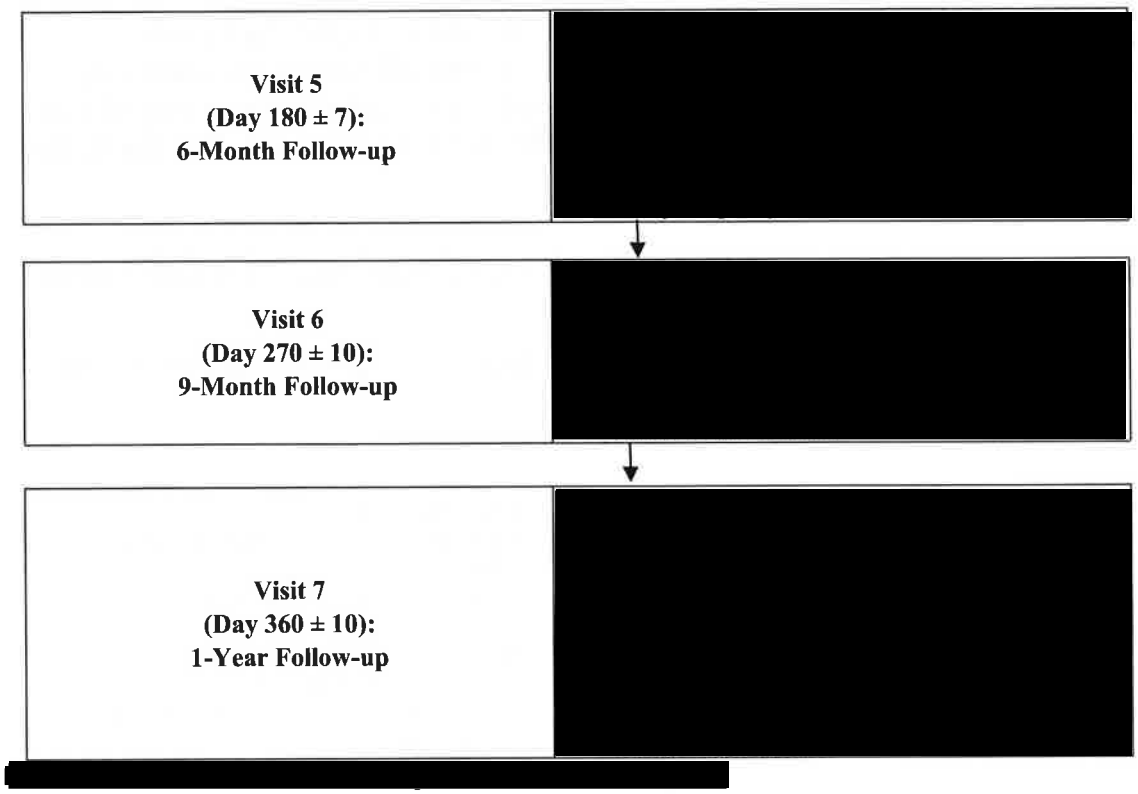
- 0.25% Reproxalap Ophthalmic Solution (reproxalap)
- Vehicle Ophthalmic Solution (vehicle)

Approximately 850 subjects will be randomly assigned to one of the two treatment groups (2:1) to receive either reproxalap or vehicle as topical ophthalmic drops administered bilaterally QID for four weeks followed by BID dosing for weeks 5-6. Approximately 550 subjects will dose QID for four weeks and continue dosing BID for the following 11 months. Subjects, Sponsor, CRO, and site personnel will be masked to treatment assignment.

All subjects will dose with randomized treatment QID between Visit 1 and Visit 2 and switch to BID dosing between Visit 2 and Visit 4 or between Visits 2 and Visit 7 for the long-term follow-up group.

The total number of expected participants, including screen failures, is approximately 1050 subjects.

A study flow chart appears below:



Subjects who terminate early during the treatment period will be asked to complete safety assessments prior to commencement of alternative DED therapy (if possible).

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

It is estimated that approximately 1050 subjects will be screened to enroll approximately 850 subjects in a 2:1 ratio of reproxalap to vehicle. Approximately550 subjects will continue after Week 6 for long-term follow-up, with the goal of at least 100 reproxalap subjects completing the long-term follow-up.

5.2 Study Population Characteristics

All subjects must be at least 18 years of age, of either gender, and of any race, and must meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Subjects must meet all of the following criteria:

1. At least 18 years of age (either gender and any race);
2. Ability to provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form;
3. Reported history of dry eye for at least 6 months prior to Visit 1;
4. History of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1;

[redacted]

5.4 Exclusion Criteria

Subjects must not meet any of the following criteria:

1. Clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation, or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;
2. Diagnosis of an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;
3. Contact lens use within 7 days of Visit 1 or anticipate using contact lenses during the trial;
4. Eye drop use within 2 hours of Visit 1;
5. Previous laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months;

[redacted]

7. Planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1;
8. Temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;

9. Use of and unwillingness to discontinue topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs for the duration of the trial (excluding medications allowed for the conduct of the trial);

[redacted]

11. Pregnancy, nursing, or planned pregnancy during the conduct of the trial;

12. Unwillingness to submit a urine pregnancy test at Visit 1 and Visit 3 (6-week subjects)/Visit 7 (LTFU subjects) (or early termination visit) if of childbearing potential. (Nonchildbearing potential is defined as a woman who is permanently sterilized [e.g., has had a hysterectomy or tubal ligation], or is post-menopausal [without menses for 12 consecutive months];

13. If of childbearing potential, unwillingness to use an acceptable means of birth control. (Acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device [IUD]; or surgical sterilization of partner. For non-sexually active males or females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, he/she must agree to use adequate birth control as defined above for the remainder of the trial.);

14. Known allergy and/or sensitivity to the test article or its components;

15. A condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study;

16. Abnormal endothelial cell count (LTFU subjects only);

17. Current enrollment in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;

18. Previous reproxalap use within the past year; Inability or unwillingness to follow instructions, including participation in all study assessments and visits.

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw consent from the study at any time.

Sponsor and/or investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.6.2).

6 STUDY PARAMETERS

6.1 Primary Safety Endpoints

- Proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP
- Proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP
- Proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP
- Proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP

6.2 Other Safety Endpoints

- Visual acuity
- Slit-lamp evaluation
- Adverse event query
- Intraocular Pressure (IOP)
- Dilated fundoscopy
- Central Cornea Endothelial Cell Counts (1-year LTFU subjects only)
- Blood chemistry and hematology analysis in a subset of subjects (1-year LTFU subjects only)
- Unanesthetized Schirmer's Test

[redacted]

6.3 Other Measures

- Urine Pregnancy Test

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Study Drug(s)/ Formulation(s)

- 0.25% Reproxalap Ophthalmic Solution (reproxalap)

- Vehicle Ophthalmic Solution (vehicle)

7.1.2 Study Drug Packaging Configuration

Study drug and vehicle vials are packaged in 5 count pouches, which will then be packaged into kits that will supply for 2-week periods. These kits will be made of 14 of the 5 count pouches.

7.1.3 Study Drug Storage and Accountability

The study drug must be stored in a secure area accessible only to the investigator and his/her designees. The study drug will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. [redacted]

[redacted]

The study drug is to only be prescribed by the principal investigator or his/her named sub investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drug by maintaining a detailed inventory. This includes the amount of study drug received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

7.1.4 Instructions for Dispensation, Use, and Administration

[redacted]

- The vehicle solution consists of all components of the drug product solution with the exception of reproxalap.
- At the study site, all Investigational Product (IP) must be stored under the conditions specified in the Investigator's Brochure in a secure area accessible only to the designated qualified clinical site personnel. All IP must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, International Council on Harmonisation (ICH) Good Clinical Practices (GCPs) and study procedures.

[redacted]

[redacted]

- Subjects will receive 3 treatment kits or 14 treatment kits (Long-Term Follow-up Group). After Visit 2 all subjects will change their dosing regimen from QID to BID for the remainder of the treatment period.
- At a minimum, the immediate or secondary study drug packaging will provide the following information: study Sponsor identification, directions for use, required storage conditions, caution statements (including "New Drug–Limited by Federal Law to Investigational Use" language), and study identification.

7.2 Other Study Supplies

Other study supplies include urine pregnancy tests, Schirmer's test strips, sodium fluorescein, Fluress, and Tropicamide.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in Sections 5.2, 5.3, and 5.4 will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., prior to changes in a subject's medical treatment and/or prior to study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an informed consent form (ICF). The informed consent form must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board (IRB).

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the Exclusion Criteria (Section 5.4).

8.1.4 Procedures for Final Study Entry

Subjects must meet all inclusion and none of the exclusion criteria.

8.1.5 Methods for Assignment to Treatment Groups:

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

At Visit 1, a patient who meets all the eligibility criteria will be randomized to receive treatment 0.25% Reproxalap Ophthalmic Solution or placebo in a 2:1 ratio by the IWRS.

The Interactive Web Response System (IWRS) will assign the randomization number and the assigned kit number for the patient. The site staff will dispense to the patient the study kit labeled with the corresponding kit number. Randomization will be stratified by follow-up schedule (6-week follow-up vs 1-year follow-up). Both the randomization number and the dispensed study drug kit number will be recorded on the patient's source document and eCRF.

8.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 5.4).

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objective(s)

The following procedures will be performed (see Appendix 2 for description):

Visit 1 (Day 1): Screening & Randomization

- Informed consent / Health Information Portability and Accountability Act (HIPAA);

[redacted]

- Qualified subjects will be scheduled for Visit 2.

Visit 2 (Day 29 ±3 days): 4-Week Follow-up

- Schedule subjects for Visit 3.

Visit 3 (Day 43 ± 4 days): 6-Week Follow-Up

- Schedule subjects for Visit 4.

Visit 4 (Day 90 ± 7 days): 3-Month Follow-up

Long-Term Follow-up (LTFU) Subjects Only

Visit 5 (Day 180 ± 7 days): 6-Month Follow-up

Long-Term Follow-up (LTFU) Subjects Only

Schedule subjects for Visit 6.

Visit 6 (Day 270 ± 10 days): 9-Month Follow-up

Long-Term Follow-up (LTFU) Subjects Only

- Schedule subjects for Visit 7.

Visit 7 (Day 360 ± 10 days): 1-Year Follow-up

Long-Term Follow-up (LTFU) Subjects Only

- Study Exit

Early Termination/Discontinuation

If a subject is discontinued from the study prior to Visit 7 (Day 360 ± 10), then all safety evaluations that are to be performed at Visit 7 should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

Adverse Events (both elicited and observed) and SAEs will be monitored throughout the study. The investigator will promptly review all adverse events (both elicited and observed) for accuracy and completeness. All adverse events will be documented on the appropriate source document and eCRF. If a female reports a pregnancy or has a positive pregnancy test during the study, then the investigator will notify [redacted] immediately. The investigator shall instruct the patient to immediately stop the study medication and request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to [redacted]

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

These visits may be performed in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

8.5 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of study drug at the end of each visit (except the subject's final visit) and given written instructions. The subject's used and unused study drug ampules will be collected at each visit from Visit 2 up to and including Visit 3 or Visit 7 (Long-Term Follow-up subjects) to assess dosing compliance. Dosing compliance will be based on the unused ampule count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of unused ampules, then the subject will be deemed non-compliant and a dosing deviation should be recorded.

These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

8.6.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study due to:

- adverse events;
- protocol violations;
- administrative reasons (e.g., inability to continue due to scheduling changes);
- lost to follow up;
- sponsor termination of study;
- subject choice (e.g. withdrawal of consent); and
- other

Note: In addition, any subject may be discontinued for any sound medical reason at the discretion of the investigator.

Discontinuations that are the direct result of SARS-CoV-2 (COVID-19) will be classified separately and clearly documented in the eCRF. A separate field will be completed to denote a COVID-19 related discontinuation and the specific reason will be documented utilizing the above noted list of subcategories.

Notification of a subject discontinuation and the reason for discontinuation will be made to [redacted] study sponsor and will be clearly documented on the eCRF.

8.7 Study Termination

The study may be stopped at any time by the investigator, the sponsor, [redacted] with appropriate notification.

8.8 Study Duration

An individual subject's participation will involve either 3 visits over approximately a 6-week period (42 days) or 7 visits over approximately a year (360 days).

8.9 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability and storage conditions, subject safety, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, [redacted] quality assurance, the sponsor and/or its designees may carry out on-site inspections and/or audits, which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered IP-related. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the 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. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the CRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Any pre-existing medical condition that worsens after administration of the IP will also be considered a new adverse event.

If there is a worsening of a medical condition that was present prior to the administration of the IP, this should also be considered a new adverse event and reported. Any medical condition present prior to the administration of the IP that remains unchanged or improved should not be recorded as a treatment emergent adverse event at subsequent visits unless it worsens during treatment.

Investigational Product (IP) includes the investigational drug under evaluation and placebo, or any other medications required by the protocol given during any stage of the study.

Documentation regarding the adverse event should be made as to the nature, date of onset, end date, severity, relationship to IP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

9.1.1 Severity

Severity of an adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by the investigator or reported to him/her by the patient/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]

9.1.2 Relationship to Investigational Product

The relationship of each adverse event to the Investigational Product (IP) should be determined by the investigator using these explanations:

- *Definite*: When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product 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.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the IP caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the adverse event. Types of evidence that would suggest a causal relationship between the IP and the adverse event include: a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an adverse event should be determined based upon existing safety information about the IP using these explanations:

- *Unexpected*: An adverse event that is not listed in the Investigator's brochure or is not listed at the specificity or severity that has been observed.
- *Expected*: An adverse event that is listed in the Investigator's brochure at the specificity and severity that has been observed.
- *Not Applicable*: Any adverse event that is unrelated to the IP.

Adverse events that are mentioned in the Investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an adverse event, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An adverse event 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 life-threatening, or 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.

9.3 Procedures for Reporting Adverse Events

All adverse events and their outcomes must be reported to [redacted] the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All adverse events that are 'suspected' and 'unexpected' are to be reported to [redacted] the study sponsor and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all serious adverse events, regardless of relationship to the study drug, must be immediately reported. All information relevant to the serious adverse event must be recorded on the appropriate eCRF. The investigator is obligated to pursue and obtain information requested by [redacted] and/or the sponsor in addition to that information reported on the eCRF. All subjects experiencing a serious adverse event must be followed up and the outcome reported.

In the event of a serious adverse event, the investigator must notify [redacted] and the sponsor immediately (within 24 hours); obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide [redacted] the study sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB of the adverse event within their guidelines for reporting serious adverse events.

Serious adverse events should be reported within one day to the contacts listed below:

Name Title: Company: Mobile Phone: Email:	[redacted]
Name Title: Office Telephone: Mobile Phone: Office Facsimile:	[redacted]

9.4 Procedures for Unmasking of Study Drug

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), [redacted] and/or the study sponsor should be notified 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 [redacted] and/or the medical monitor prior to unmasking the identity of the IP, if possible. [redacted] will ask the site to complete and send them the Unmasking Request Form. [redacted] 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 using IWRS. 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.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

Adverse events that are ongoing at the end of the study visit will be followed. Phone calls will be placed with any subject who experiences an adverse event until the issue is resolved or the condition is considered ongoing and stable.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

Safety Population – The safety population will include all subjects receiving treatment from whom at least one safety measurement is obtained following the first dose of study drug. The safety population will be analyzed for all safety assessments.

Safety-LTFU Population – The Safety population will include all LTFU subjects receiving treatment from whom at least one safety measurement is obtained following the first dose of study drug. The Safety-LTFU population will be analyzed for all safety assessments. Subjects in the Safety-LTFU population will be analyzed as treated. Subjects in the Safety population will be analyzed as treated.

10.2 Statistical Hypotheses

The following statistical hypotheses will be tested:

Safety Population at 6 weeks:

H_{01}: There is no difference in the proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP in the 0.25% Reproxalap group vs. Vehicle group in the Safety population within 6 weeks of study drug treatment.

H_{A1}: The proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP is greater in the 0.25% Reproxalap group than the Vehicle group in the Safety population within 6 weeks of study drug treatment.

H_{02}: There is no difference in the proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP in the

0.25% Reproxalap group vs. Vehicle group in the Safety population within 6 weeks of study drug treatment.

H_{A2}: The proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP is greater in the 0.25% Reproxalap group than the Vehicle group in the Safety population within 6 weeks of study drug treatment.

H_{03}: There is no difference in the proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP in the 0.25% Reproxalap group vs. Vehicle group in the Safety population within 6 weeks of study drug treatment.

H_{A3}: The proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP is greater in the 0.25% Reproxalap group than the Vehicle group in the Safety population within 6 weeks of study drug treatment.

H_{04}: There is no difference in the proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP in the 0.25% Reproxalap group vs. Vehicle group in the Safety population within 6 weeks of study drug treatment.

H_{A4}: The proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP is greater in the 0.25% Reproxalap group than the Vehicle group in the Safety population within 6 weeks of study drug treatment.

Long-Term Follow-up Subjects at (6 Months or 1 Year)

H_{05}: There is no difference in the proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP in the 0.25% Reproxalap group vs. Vehicle group in the Safety-LTFU population within 6 months of study drug treatment (or 1 year).

H_{A5}: The proportion of subjects that experience that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP is greater in the

0.25% Reproxalap group than the Vehicle group in the Safety-LTFU population within 6 months of study drug treatment (or 1 year).

H_{06}: There is no difference in the proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP in the 0.25% Reproxalap group vs. Vehicle group in the Safety-LTFU population within 6 months of study drug treatment (or 1 year).

H_{A6}: The proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP is greater in the 0.25% Reproxalap group than the Vehicle group in the Safety-LTFU population within 6 months of study drug treatment (or 1 year).

H_{07}: There is no difference in the proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP in the 0.25% Reproxalap group vs. Vehicle group in the Safety-LTFU population within 6 months of study drug treatment (or 1 year).

H_{A7}: The proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP is greater in the 0.25% Reproxalap group than the Vehicle group in Safety-LTFU population within 6 months of study drug treatment (or 1 year).

H_{08}: There is no difference in the proportion of subjects at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP in the 0.25% Reproxalap group vs. Vehicle group in the Safety-LTFU population within 6 months of study drug treatment (or 1 year).

H_{A8}: The proportion of subjects at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP is greater in the 0.25% Reproxalap group than the Vehicle group in the Safety-LTFU population within 6 months of study drug treatment (or 1 year).

10.3 Sample Size

6 Week:

[redacted]

[redacted]

Table 1: Assumed True Event Proportions

[redacted]

[redacted]

[redacted]

6 Months (26 weeks) and 1 Year:

[redacted]

[redacted]

Table 2: Assumed True Event Proportions

[redacted]

10.4 Statistical Analysis

10.4.1 General Considerations

Quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The dichotomous variables will be summarized using counts and percentages.

Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

Baseline measures are defined as the last measure prior to the administration of study treatment at Visit 1 (Day 1). Change from baseline will be calculated as Visit – Baseline.

For the purpose of summarization, medical history, concurrent therapies, and AEs will be coded to MedDRA and WHO Drug dictionaries, as appropriate.

10.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For subject-level efficacy endpoints, the unit of analysis will be the subject. For endpoints assessed on each eye individually, the unit of analysis will be right eye (OD) or left eye (OS).

10.4.3 Missing Data

All primary and other safety analyses will be executed using observed data only for both Safety Population and Safety-LTFU population. Sensitivity analyses including treatment of missing data will be outlined in the SAP.

10.4.4 Multiplicity Adjustments

[redacted]

10.4.5 Primary Safety Analyses

[redacted]

The primary safety comparisons in this trial will be between 0.25% Reproxalap versus Vehicle in the Safety Population using the following primary estimand:

Estimand 1

- Populations:
  - Subjects with DED defined through enrollment criteria that are enrolled in either the 6-week follow-up or 1-year follow-up schedule.
  - Subjects with DED defined through enrollment criteria that are enrolled in the 1-year follow-up schedule only.
- Endpoints:

  Safety population at 6 weeks:

  - Proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP within 6 weeks of study drug dosing in the Safety population
  - Proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP within 6 weeks of study drug dosing in the Safety population
  - Proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP within 6 weeks of study drug dosing in the Safety population
  - Proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP within 6 weeks of study drug dosing in the Safety population

  Safety-LTFU population within 6 months (or 1 year):

  - Proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP within 6 months/1 year of study drug dosing in the Safety-LTFU population
  - Proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP within 6 months/1 year of study drug dosing in the Safety-LTFU population
  - Proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP within 6 months/1 year of study drug dosing in the Safety-LTFU population
  - Proportion of subjects that experience at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP

within 6 months/1 year of study drug dosing in the Safety-LTFU population

- Intercurrent event:
  - Discontinuation of study medications is ignored, measures obtained after discontinuation of study medication will be analyzed. [treatment policy strategy]
  - Non-optimal compliance is ignored, measures will be analyzed regardless of treatment compliance. [treatment policy strategy]
  - Use of prohibited alternative therapies is ignored, measures obtained after initiation of prohibited therapies will be analyzed. [treatment policy strategy]
  - Discontinuation of study, subjects that discontinue study prior to time point of interest for an endpoint (Ex. 6 weeks or 6 months/1 year) AND do not experience event of interest will not be analyzed. [principal stratum strategy]
  - Discontinuation of study, values post-discontinuation will not be imputed. [while on treatment strategy]
- Population-level summaries:
  - Difference in the proportion of subjects that experience at least one TE-SAE of a visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) categorized as probably or definitely related to IP
  - Difference in the proportion of subjects that experience at least one TE-SAE of an IOP increase from baseline of $\geq$ 10 mm Hg AND report an IOP of > 25 mm Hg categorized as probably or definitely related to IP
  - Difference in the proportion of subjects that experience at least one TE-SAE of the cornea detected via slit-lamp biomicroscopy categorized as probably or definitely related to IP
  - Difference in the proportion of subjects with at least one TE-SAE of the retina detected via fundoscopy categorized as probably or definitely related to IP

Sensitivity analyses of the primary safety endpoints may include repeating primary analyses with alternative handling of intercurrent events with different estimands. In addition, sensitivity analyses using incidence rates (events/person-time) will be produced. Details will be outlined in the SAP.

10.4.6 Other Safety Analyses

Dosing information will be summarized overall subjects and listed for each subject will be listed. Discontinuation of treatment will be summarized by treatment received. The primary reason for trial drug discontinuation will also be summarized by treatment received.

Adverse events (AEs) will be coded using the MedDRA dictionary. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment.

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature treatment discontinuation will be provided by treatment group. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term for the following categories of AEs:

- All TEAEs
- TEAEs at least possibly related to study treatment
- TEAEs leading to study treatment discontinuation
- Serious TEAEs
- By maximal severity
- By study day of onset

Separate analyses will be performed for ocular and non-ocular AEs. Separate analyses of AEs will be generated for the Safety population with 6 weeks of follow-up and the Safety-LTFU population with 6 months of follow-up (or 1 year of follow-up).

Other safety endpoints will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. Separate analyses will be generated for the Safety population with 6 weeks of follow-up and the Safety-LTFU population with 6 months of follow-up (or 1 year of follow-up).

Assessments performed by eye will be summarized separately for right eye and left eye.

[redacted]

10.4.8 Interim Analyses

[redacted]

[redacted]

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject prior to enrollment into the study.

All informed consent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB approved version of the informed consent form will be used.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions

as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of [redacted] the sponsor, the IRB approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and EKGs. The investigator's copy of the eCRF serves as the investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study-related source documents, correspondence, patient records, consent forms, record of the distribution and use of all study drug and copies of case report forms should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

11.5.1 Labeling/Packaging

Investigational drug will be packaged and labeled into clinical kits.

For the treatment period, 14 pouches will be packaged in a 2-week clinical kit. Each patient will receive the appropriate number kits for the duration

of the trial they are assigned (3 kits for the six week and fourteen for one year). Each pouch will contain five ampules to provide a sufficient supply of randomized study drug.

11.5.2 Storage of Study Drug

The study drug must be stored in a secure area accessible only to the investigator and his/her designees. The study drug will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. [redacted]

11.5.3 Accountability of Study Drug

The study drug is to only be prescribed by the principal investigator or his/her named sub investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drug by maintaining a detailed inventory. This includes the amount of study drug received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

11.5.4 Return or Disposal of Study Drug

All study drug will be returned to the sponsor or their designee or destroyed on behalf of the Sponsor following local regulations.

11.6 Recording of Data on Source Documents and electronic Case Reports Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction

and when, by adding to the correction his/her initials as well as the date of the correction

11.7 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript.

[redacted]

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13 APPENDICES

Appendix 1: Schedule of Visits and Measurements

6 Week Follow-Up Subjects

Visit	Visit 1 Day 1	Visit 2 Day 29 ± 3	Visit 3 Day 43 ± 4
Procedure	**Screening & Randomization**	**Follow-up Visit**	**Follow-up Visit**
Informed Consent / HIPAA	X		
[redacted]		X	X
[redacted]	X		
[redacted]		X	X
[redacted]		X	X
[redacted]		X	X
[redacted]	X	X	X
[redacted]	X[1]		X[1]
[redacted]	X		
[redacted]	X	X	X
[redacted]	X		
[redacted]	X	X	X
[redacted]	X		
[redacted]	X	X	X
[redacted]	X	X	X
[redacted]	X		
[redacted]	X		
[redacted]	X		
[redacted]	X	X	
[redacted]	X	X	
[redacted]			X

Long Term Follow Up Subjects

Visit	Visit 1 Day 1	Visit 2 Day 29 ± 3	Visit 3 Day 43 ± 4	Visit 4 Day 90 ± 7	Visit 5 Day 180 ± 7	Visit 6 Day 270 ± 10	Visit 7 Day 360 ± 10
Procedure	**Screening & Randomization**	**Follow-up Visit**	**Follow-up Visit**	**Follow-up Visit**	**Follow-up Visit**	**Follow-up Visit**	**Follow-up Visit**
Informed Consent / HIPAA	X						
[redacted]		X	X	X	X	X	X
[redacted]	X						
[redacted]		X	X	X	X	X	X
[redacted]		X	X	X	X	X	X
[redacted]		X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X
[redacted]							X[2]
[redacted]	X[1]						X[1]
[redacted]	X						X
[redacted]	X	X	X	X	X	X	X
[redacted]	X						
[redacted]	X	X	X	X	X	X	X
[redacted]	X						X
[redacted]	X				X		X
[redacted]	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X
[redacted]	X						
[redacted]	X						
[redacted]	X						
[redacted]	X	X	X	X	X	X	
[redacted]	X	X	X	X	X	X	
[redacted]							X

[redacted]

Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

The following examination procedures, tests, equipment and techniques are listed in this Appendix:

Visual Acuity Procedures

[redacted]

Slit-lamp Biomicroscopy

Unanesthetized Schirmer's Test

Procedure for Evaluating Intraocular Pressure

[redacted]

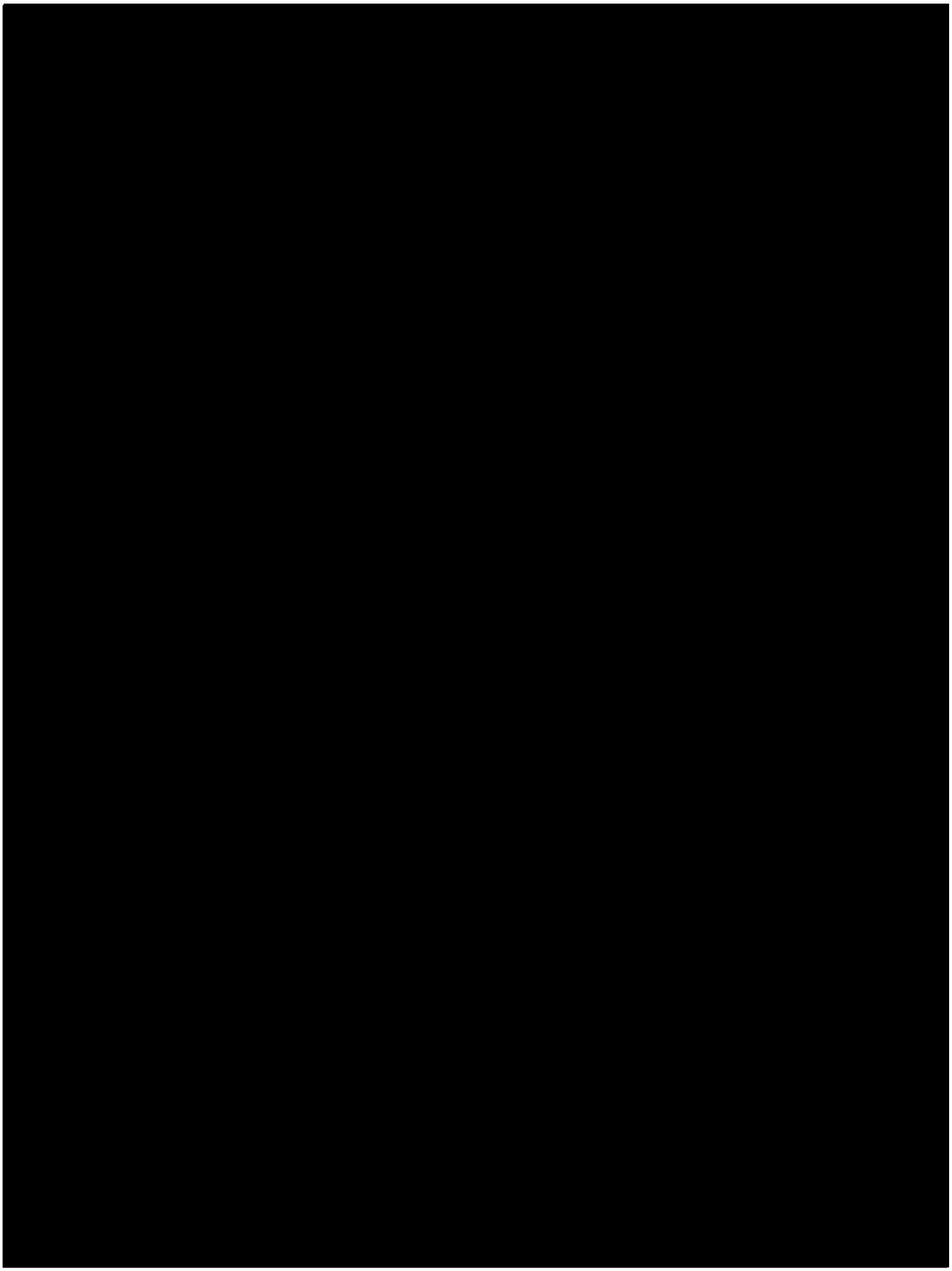
Procedure for Conducting Dilated Fundoscopy

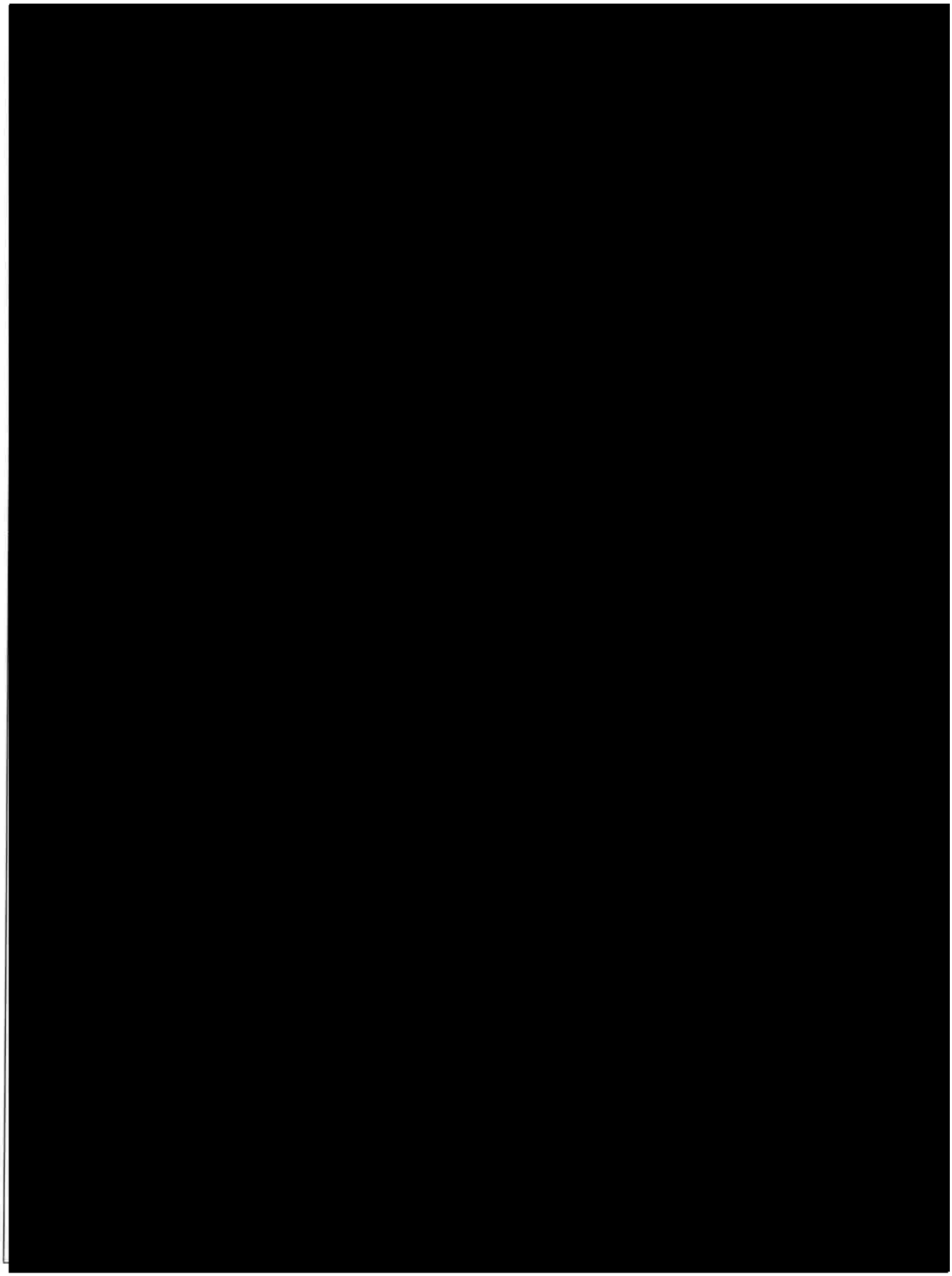
Specular Microscopy

Blood Chemistry and Hematology

Appendix 3: Protocol Amendment Summary

[redacted]





Appendix 4: Sponsor and Ora Approvals

Protocol Title: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Clinical Trial Evaluating the Safety of 0.25% Reproxalap Ophthalmic Solution in Subjects with Dry Eye Disease

Protocol Number: ADX-102-DED-021

Amendment 3 Date: 16 August 2022

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

[redacted]

Appendix 5: Investigator's Signature

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Clinical Trial Evaluating the Safety of 0.25% Reproxalap Ophthalmic Solution in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-021
Amendment 3 Date:	16 August 2022

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by [redacted] and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____