Clinical Trial Protocol: ADX-102-DED-032

Protocol Title:	A Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-032
Study Phase:	3
Test Article Name:	0.25% Reproxalap Ophthalmic Solution
IND Number:	134734
Indication:	Dry Eye Disease
Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Ave. Lexington, MA 02421 USA
IRB/IEC:	[redacted]

	Date
Original Protocol:	19Apr2024

Confidentiality Statement
This protocol contains confidential, proprietary information [redacted] and Aldeyra Therapeutics, Inc. Further dissemination, distribution, or copying of this protocol or its contents is strictly prohibited.

STUDY PERSONNEL

SPONSOR PERSONNEL

Chief Development Officer:	[redacted]
[redacted]	
Department Senior Vice President:	[redacted]
Department Senior Director:	[redacted]
Clinical Project Manager:	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Protocol Title:	A Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-032
Test Article:	0.25% Reproxalap Ophthalmic Solution (reproxalap)
Study Phase:	3
Primary Objective(s):	To evaluate the efficacy of reproxalap, as assessed by an ocular symptom during exposure to the [redacted] (CAE) in subjects with dry eye disease
Overall Study Design:	
Structure:	Double-masked, randomized, parallel-group trial
Duration:	Approximately 16-32 days per subject
Controls:	Vehicle Ophthalmic Solution (vehicle)
Dosage:	Vehicle will be administered once approximately 5 minutes prior to the CAE entry and once approximately 50 minutes after initiation of the CAE at Visit 1. Test article will be dosed topically in both eyes. Test article will be administered four times (QID) at Visit 2. At Visit 3, test article will be administered once approximately 5 minutes prior to CAE entry and once approximately 50 minutes after initiation of the CAE.
Summary of Visit Schedule:	Three visits over the course of approximately 2 weeks: • Visit 1 = Day -14 -16/+2, screening, vehicle CAE • Visit 2 = Day 1, randomization, QID test article administration • Visit 3 = Day 2,test article CAE, trial exit At Visit 2, subjects will be randomized 1:1 to receive either reproxalap or vehicle for Visit 2 and Visit 3.
Measures Taken to Reduce Bias:	ADX-102-DED-032 is a randomized treatment assignment, double-masked trial.
Study Population Characteristics:	

Number of Subjects:	Approximately 110 subjects are expected to be enrolled in the trial.
Inclusion Criteria:	Subjects must meet all of the following criteria: 1. 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 ocular discomfort associated with dry eye disease for at least 6 months prior to Visit 1; 4. Reported 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: [redacted] 2. Clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction, lid margin inflammation, or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters; 3. Diagnosis of an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1; 4. Contact lens use within 7 days of Visit 1 or anticipated use of contact lenses during the trial; 5. Artificial tear eye drop use within 2 hours of Visit 1 or within 24 hours of Visit 2 (drops cannot be used on the day of Visit 2 or Visit 3); 6. Previous laser-assisted *in situ* keratomileusis surgery within the last 12 months;

	7. Use of topical ocular cyclosporine, lifitegrast, or corticosteroid within 90 days of Visit 1; 8. Systemic corticosteroid or other immunomodulator therapy (not including inhaled corticosteroids) within 14 days of Visit 1, or any planned immunomodulatory therapy throughout the clinical trial; 9. Planned ocular and/or lid surgeries throughout the clinical trial or any ocular surgery within 6 months of Visit 1; 10. Temporary punctal plugs during the trial that have not been stable within 30 days of Visit 1; 11. Use of and unwillingness to discontinue topical ophthalmic prescriptions (including medications for glaucoma) or over-the-counter solutions (not including artificial tears), gels, or scrubs for the duration of the trial (excluding medications allowed for the conduct of the trial); 12. Corrected visual acuity greater than or equal to logarithm of the minimum angle of resolution (logMAR) + 0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1; 13. Pregnancy, nursing, or planned pregnancy during the conduct of the trial; 14. Unwillingness to submit a urine pregnancy test at Visit 1 and Visit 3 (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].); 15. If of childbearing potential (female or male), 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 trial, he/she must agree to use adequate birth control as defined above for the remainder of the trial.);

	16. Known allergy and/or sensitivity to the test article or test article components; 17. A condition that the investigator feels may put the subject at significant risk, may confound the trial results, or may interfere significantly with participation in the trial; 18. Current enrollment in an investigational drug or device trial or previous use of an investigational drug or device within 30 days of Visit 1; [redacted] 20. Current use of any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1; or 21. Inability or unwillingness to follow instructions, including participation in all assessments and visits.
Evaluation Criteria:	
Primary Endpoint:	Ocular discomfort symptom score (0 – 100 VAS) over 100 minutes in the CAE at Visit 1 and Visit 3
Safety Endpoints:	• Visual acuity • Slit lamp examination • Adverse event query • Intraocular pressure

General Statistical Methods and Types of Analyses:

Statistical analyses will be detailed in the statistical analysis plan, which will dominate any statistical language herein. Any changes to protocol-stated analyses will also be detailed in the statistical analysis plan.

Sample Size:

[redacted]

Primary Efficacy Analysis:

The primary endpoint will be assessed using the intent-to treat (ITT) population with observed data only. The ITT population includes all randomized subjects.

[redacted]

[redacted]

Safety Analyses:

Safety endpoints will be summarized using descriptive statistics. For qualitative safety assessments, counts and percentages will be reported at the eye level and subject level, where appropriate. For quantitative safety assessments, endpoints will be summarized at the eye level using continuous summary statistics.

Summary of Known and Potential Risks and Benefits to Human Subjects:

Potential risks and benefits are described in the Investigator's Brochure.

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List of Abbreviations

[redacted]	[redacted]
CFR	Code of Federal Regulations
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	institutional/independent review board
ITT	intent-to-treat
LogMAR	logarithm of the minimum angle of resolution
MMRM	mixed model repeated measures
[redacted]	[redacted]
OTC	over the counter
PP	per protocol
QID	four times daily
RASP	reactive aldehyde species
TEAE	treatment-emergent adverse event
VAS	visual analog scale

1 INTRODUCTION

[redacted]

2 STUDY OBJECTIVE

To evaluate the efficacy of reproxalap, as assessed by an ocular symptom (ocular discomfort) during exposure to the CAE in subjects with dry eye disease.

3 CLINICAL HYPOTHESES

The clinical hypothesis is that reproxalap is more effective than vehicle in reducing subject-reported ocular discomfort.

4 OVERALL STUDY DESIGN

ADX-102-DED-032 is a Phase 3, randomized, double-masked, parallel-group, vehicle-controlled trial designed to evaluate the efficacy and safety of reproxalap compared to vehicle in subjects with dry eye disease. Approximately 110 subjects will be enrolled in the trial. Male and female subjects at least 18 years of age with a subject-reported history of dry eye disease and meeting all other eligibility criteria will be randomized to receive reproxalap or vehicle in a 1:1 ratio (approximately 55 subjects in each treatment arm).

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 180 subjects will be screened to enroll approximately 110 subjects across approximately 2 sites.

5.2 Study Population Characteristics

All subjects must be at least 18 years of age, be of either sex and of any race, have a subject-reported history of dry eye disease, and meet all of the inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Each subject must meet each of the following criteria:

1. 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 ocular discomfort associated with dry eye disease for at least 6 months prior to Visit 1;
4. Reported history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1;

[redacted]

5.4 Exclusion Criteria

Each subject may <u>not meet any of the following criteria</u>:

[redacted]

2. Clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction, lid margin inflammation, or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with trial parameters;
3. Diagnosis of an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;
4. Contact lens use within 7 days of Visit 1 or anticipated use of contact lenses during the trial;
5. Artificial tear eye drop use within 2 hours of Visit 1 or within 24 hours of Visit 2 (drops cannot be used on the day of Visit 2 or Visit 3;
6. Previous laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months;
7. Use of topical ocular cyclosporine, lifitegrast, or corticosteroid within 90 days of Visit 1;
8. Systemic corticosteroid therapy or other immunomodulator (not including inhaled corticosteroids) within 14 days of Visit 1 or anticipate such therapy throughout the clinical trial;
9. Planned ocular and/or lid surgeries throughout the clinical trial or any ocular surgery within 6 months of Visit 1;
10. Temporary punctal plugs during the trial that have not been stable within 30 days of Visit 1;
11. Use of and unwillingness to discontinue topical ophthalmic prescriptions (including medications for glaucoma) or over-the-counter solutions (not including artificial tears), gels or scrubs for the duration of the trial (excluding medications allowed for the conduct of the trial);
12. Corrected visual acuity greater than or equal to logarithm of the minimum angle of resolution (logMAR) + 0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1;
13. Pregnancy, nursing, or planned pregnancy during the conduct of the trial;
14. Unwillingness to submit a urine pregnancy test at Visit 1 and Visit 3 (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]);

15. If of childbearing potential (female or male), 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 trial, he/she must agree to use adequate birth control as defined above for the remainder of the trial);
16. Known allergy and/or sensitivity to the test article or test article components;
17. A condition that the investigator feels may put the subject at significant risk, may confound the trial results, or may interfere significantly with participation in the trial;
18. Current enrollment in an investigational drug or device trial or previous use of an investigational drug or device within 30 days of Visit 1;
19. [redacted]
20. Current use of any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1; or
21. Inability or unwillingness to follow instructions, including participation in all assessments and visits.

5.5 Withdrawal Criteria (if applicable)

Subjects may voluntarily withdraw from the trial at any time. Additionally, subjects may be discontinued for safety reasons as determined by the investigator and/or Medical Monitor.

6 STUDY PARAMETERS

6.1 Primary Endpoint

Ocular discomfort symptom score (0 – 100 VAS) over 100 minutes in the CAE at Visit 1 and Visit 3

6.2 Safety Endpoints

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

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Test Article and Vehicle Packaging Configuration

[redacted]

7.1.2 Test Article Storage and Accountability

[redacted]

The test article is to be used only in accordance with this protocol. The test article must be distributed only to subjects properly qualified under this protocol to receive test article. The investigator must keep an accurate accounting of the test article by maintaining a detailed inventory, including the amount of test article received by the site, amount used, and the amount returned to the Sponsor upon the completion of the trial.

7.1.3 Instructions for Dispensation, Use, and Administration

- At Visit 1, qualified subjects will be assigned a vehicle kit. Subjects will use two vials from the kit for Visit 1 in-office doses. After use, vials will be placed into a zip locked bag labeled with the subject's initials and screening number for accountability.
- At Visit 2, qualified subjects will be randomized and will be assigned a single kit of reproxalap or vehicle. Subjects will be dosed at the clinical site four times. (3 hours between Dose 1 and Dose 2, 30 minutes between Dose 2 and Dose 3, 30 minutes between Dose 3 and Dose 4) by trained site staff.
- At Visit 3, subjects will be dosed two times at the clinical site (approximately 5 minutes prior to CAE entry and approximately 50 minutes after CAE entry) from the same kit by trained site staff.
- Subjects will be instructed to close their eyes for two minutes after instillation.

7.2 Other Study Supplies

[redacted]

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in section 5.2, 5.3, and 5.4 will be considered for entry into the trial.

8.1.2 Informed Consent

Prior to participation in the clinical trial, the clinical trial will be discussed with the subjects, and subjects wishing to participate must give written informed consent using an informed consent form. The informed consent form must be the most recent version that has received approval/favorable review by a properly constituted Independent Review Board.

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the exclusion criteria.

8.1.4 Procedures for Final Study Entry

Subjects must satisfy all of the inclusion criteria and none of the exclusion criteria in order to be entered into the trial.

8.1.5 Methods for Assignment to Treatment Groups:

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

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

Both the randomization number and the assigned test article kit number will be recorded on the patient's source document and electronic Case Report Form (eCRF).

8.2 Concurrent Therapies

The use of any applicable concurrent medications (prescription or OTC) is to be recorded on the subject source document along with the reason the medication was taken.

Concurrent enrollment in an investigational drug or medical device trial is not permitted.

8.2.1 Prohibited Medications/Treatments

Prohibited medications, treatments, and activities are outlined in the exclusion criteria and Appendix 2.

8.2.2 Escape Medications

Not applicable

8.2.3 Special Diet or Activities

Not applicable

8.3 Examination Procedures

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

Visit 1 (Day -14 -16/+2, screening, vehicle CAE)

- Informed consent and HIPAA
- Demographics (e.g., gender, date of birth, race, ethnicity)
- Medical/medication & ocular history
- Urine pregnancy test (as needed)
- Subject-reported ocular discomfort (0-100 VAS)
- Visual acuity (ETDRS)
- Slit lamp examination
- Fluorescein staining [redacted]
- Inclusion/exclusion criteria review
- In-office vehicle instillation by trained site staff (approximately 5 minutes prior to CAE entry)
- CAE exposure (100 minutes, vehicle administration at approximately 50 minutes) with subject-reported ocular discomfort collected at 10, 15, 20, 25, 30, 35, 40, 45, 65, 70, 75, 80, 85, 90, 95, and 100 minutes in the CAE
- CAE exit
- Slit lamp examination
- Intraocular pressure
- Schedule for Visit 2

Visit 2 (Day 1, randomization, QID test article administration)

- Medical/medication update
- Adverse event query
- Visual acuity (ETDRS)
- Slit lamp examination
- Subject-reported ocular discomfort prior to randomization (0-100 VAS)
- Inclusion/exclusion criteria review
- Randomization/enrollment
- In-office Dose #1 [redacted]

- In-office Dose # 2 [redacted]
- In-office Dose #3 [redacted]
- In-office Dose #4
- Subjects will return to clinic the following day

Visit 3 (Day 2, test article CAE, trial exit)

- Medical/medication update
- Adverse event query
- Urine pregnancy test (as needed)
- Visual acuity (ETDRS)
- Slit lamp examination
- Subject-reported ocular discomfort (0-100 VAS)
- In-office test article instillation by trained site staff (approximately 5 minutes prior to CAE entry)
- CAE exposure (100 minutes, test article administration at approximately 50 minutes) with subject-reported ocular discomfort collected at 10, 15, 20, 25, 30, 35, 40, 45, 65, 70, 75, 80, 85, 90, 95, and 100 minutes in the CAE
- CAE exit
- Slit lamp examination
- Intraocular pressure
- Trial exit

8.4 Early Termination/Discontinuation

If a subject is discontinued from the trial prior to Visit 3, then all safety evaluations that are to be performed at Visit 3 should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

Adverse events (both elicited and observed) and serious adverse events will be monitored throughout the trial. 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 case report form.

If a positive pregnancy test is observed during the trial, the investigator will notify [redacted] immediately. The investigator shall 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 the reports together with the subject's source documents and will provide a copy of all documentation to [redacted]. Pregnant subjects will be discontinued from the trial as per the exclusion criteria.

8.5 Schedule of Visits, Measurements, and Dosing

8.5.1 Scheduled Visits

Appendix 1 details the schedule of visits and measurements.

8.5.2 Unscheduled Visits

Unscheduled 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:

- Slit lamp examination;
- Visual acuity;
- Intraocular pressure;
- Urine pregnancy test;
- Assessment of adverse events;
- Assessment of concurrent medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the trial and has completed all applicable assessments.

8.6.2 Discontinued Subjects

Subjects may be discontinued prior to the completion of the trial for reason, which may include:

- Adverse events,
- Protocol violations,
- Administrative reasons (e.g., inability to continue), or
- Sponsor termination of the trial.

Notification of subject discontinuations and reasons for discontinuation will be made to [redacted] and will be clearly documented on the source document.

8.7 Study Duration

Participation in the clinical trial is estimated to be approximately 2 weeks per subject.

8.8 Monitoring and Quality Assurance

During the course of the trial, a monitor, or designee, will make routine site visits to review protocol compliance; assess test article accountability, storage conditions, and subject safety; and ensure the trial is being conducted

according to the pertinent regulatory requirements. Review of 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.

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

9 ADVERSE EVENTS

9.1 Adverse Event

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

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 by the subject. Severity assessments will be made irrespective of relationship to study procedures or seriousness of the event and will be characterized according to the following definitions:

[redacted]

9.1.2 Relationship to Study Procedures

The relationship of each adverse event to the study procedures should be determined by the investigator using the definitions below. Decisive

factors for the assessment of causal relationship of an adverse event to the study procedures include, but are not limited to, temporal relationship between the adverse event and the procedure, known side effects of the procedure medical history, and/or concomitant medication:

- *Definite:* When there are good reason and sufficient documentation to demonstrate a direct causal relationship between study procedure and adverse event;
- *Probable:* When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, or 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 (e.g., 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.

9.1.3 Expectedness

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

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

9.2 Serious Adverse Events

An adverse event is considered serious if, in the view of either the investigator or Sponsor, the adverse event 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, the occurrence of the adverse event places the subject at immediate risk of death. A life-threatening adverse event 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 ocular impairment or ocular damage (e.g., hemorrhage, retinal detachment, central corneal ulcer, or damage to the optic nerve).
- A congenital anomaly/birth defect in the fetus or child of a female subject if the subject was exposed to test article when pregnant with the fetus or child.

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, the subject may be jeopardized or may require medical or surgical intervention to prevent one of the outcomes listed above.

9.3 Procedures for Reporting Adverse Events

All adverse events and associated outcomes must be reported to [redacted] and the Institutional Review Board (IRB, as required by the IRB; federal, state, or local regulations; and governing health authorities) and recorded on the appropriate source document.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All adverse events that are related (definite, probable, possible) and unexpected are to be reported to [redacted] and the IRB, as required by the IRB; federal, state, or local regulations; and governing health authorities.

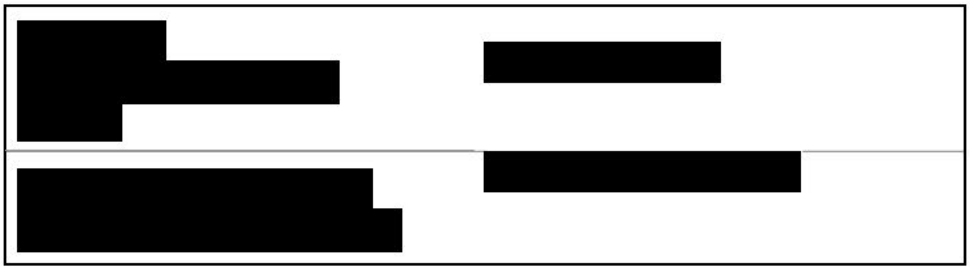
9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all serious adverse events, regardless of relationship to the test article, must be immediately reported. All information relevant to the serious adverse event must be recorded on the appropriate source

documents. The investigator is obligated to pursue and obtain information requested by [redacted] in addition to that information reported on the source document. 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] immediately; obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide [redacted] with a complete case history; and inform the IRB of the adverse event within their guidelines for reporting serious adverse events.

Contact information for reporting serious adverse events:



9.4 Procedures for Unmasking Test Article

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

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

9.5 Procedures for Reporting Adverse Events

Adverse events ongoing at the end of the trial 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

The following analysis populations will be considered:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.
- Per-Protocol Population – The per-protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations and who complete the clinical trial. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.
- Safety Population – The safety population includes all randomized subjects who have received at least one dose of test article. Subjects in the safety population will be analyzed as treated.

All analyses will be performed for the ITT population and, in addition, on the PP population as a sensitivity analysis. Descriptive statistics of safety data will be calculated for the safety population.

10.2 Statistical Hypotheses

[redacted]

10.3 Sample Size

[redacted]

10.4 General Considerations

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

All summaries will be presented by treatment arm. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

For the purpose of summarization, medical history, concurrent therapies, and adverse events will be coded to MedDRA and WHODrug dictionaries, as appropriate.

The statistical analysis plan will detail the statistical procedures and will dominate any text herein.

10.5 Unit of Analysis

Safety endpoints will be analyzed for both eyes. Subject-reported ocular discomfort will be recorded and analyzed for each eye. Assessment scales are detailed in the Appendices.

10.6 Missing Data

10.7 Multiplicity Considerations

Not applicable

10.8 Primary Efficacy Analysis

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

10.9 Safety Variables

Adverse events will be coded using the MedDRA dictionary.

Frequencies and percentages will be provided per treatment arm of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation. An adverse event is treatment-emergent if the adverse event occurs or worsens after the first dose of randomized treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest relationship, and by system organ class, preferred term, maximal severity, and strongest relationship. Separate analyses will be performed for ocular specific and all adverse events (including systemic).

Other safety endpoints, including visual acuity, slit lamp examination, and intraocular pressure, will be summarized by treatment arm and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, eyes will be summarized separately.

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

The ADX-102-DED-032 clinical trial will be conducted in compliance with the protocol, current Good Clinical Practices, and International Council for Harmonization Guidelines in a manner that is generally consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements will be followed.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any protocol-specific clinical procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the legal guardian prior to enrollment.

All informed consent/assent forms must be approved for use by [redacted] and receive approval/favorable opinion from an IRB prior to use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), to the investigator must ensure that

the amended informed consent is reviewed and approved by the Sponsor prior to submission to the governing IRB and that the amended informed consent is read, signed, and dated by all subjects currently and subsequently enrolled. If informed consent is taken under special circumstances (e.g., oral informed consent), then the consent procedures to be followed must be determined by [redacted] and provided in writing by [redacted] prior to the consent process.

11.1.2 Institutional Review Board Approval

The ADX-102-DED-032 clinical trial is to be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the trial, and must obtain re-approval at least annually.

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

11.2 Ethical Conduct of the Clinical Trial

The ADX-102-DED-032 clinical trial will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal subject data collected and processed should be maintained by the investigator and staff with adequate precautions as to ensure the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors, and other authorized representatives of [redacted], the IRB approving the trial, the United States Food and Drug Administration, the United States Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to original medical and study records for verification of the data and clinical trial procedures. Access to records will be permitted for the aforementioned individuals only to the extent permitted by law.

11.4 Documentation

Source documents may include medical records, hospital charts, clinic charts, subject files, and the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator source documents serves as the investigator record of study-related data.

11.4.1 Retention of Documentation

All trial-related correspondence, subject records, consent forms, and copies of source documents should be maintained on file for at least two years or longer, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

If an 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. [redacted] 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 Test Article

11.5.1 Labeling/Packaging

Test article will be packaged and labeled into clinical kits.

For the treatment period, two pouches will be packaged in a clinical kit. Each subject will receive one kit for the duration of the trial. Each pouch will contain five ampules.

11.5.2 Storage of Test Article

[redacted]

11.5.3 Accountability of Test Article

The test article is to be used only in accordance with the protocol. The test article must be distributed only to enrolled subjects. The investigator must keep an accurate accounting of the test article by maintaining a detailed inventory, which includes the amount of test article received by the site, amount used, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the trial.

11.5.4 Return or Disposal of Test Article

All test article will be returned to the Sponsor or a designee of the Sponsor, or destroyed on behalf of the Sponsor following local regulations.

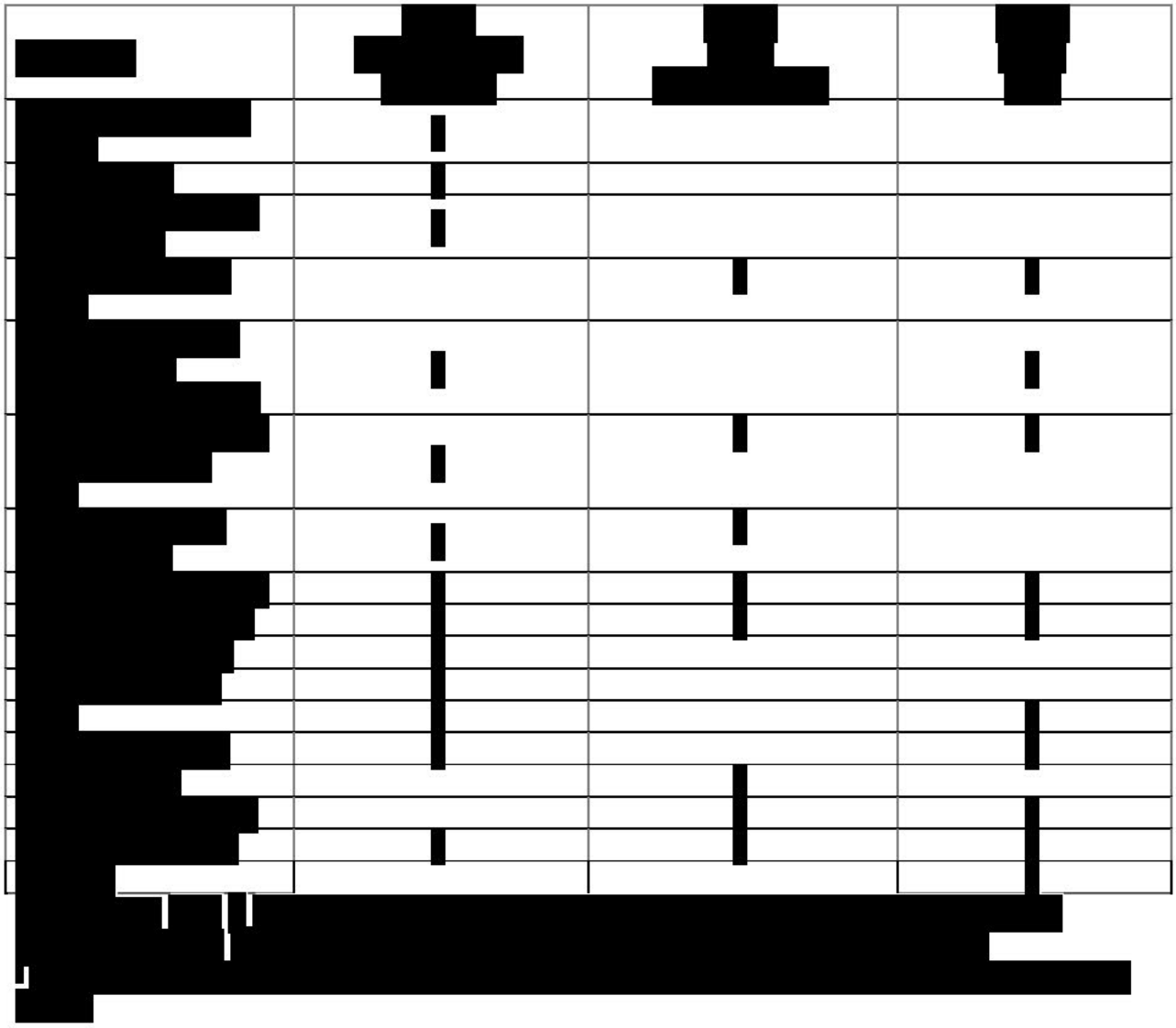
11.6 Recording of Data on Source Documents and Electronic Case Report Forms

The investigator is responsible for ensuring that data are completely and accurately recorded on each eCRF and all study-related material. All data should be attributable, legible, contemporaneous, and original. Recorded data 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 initials as well as the date of the correction.

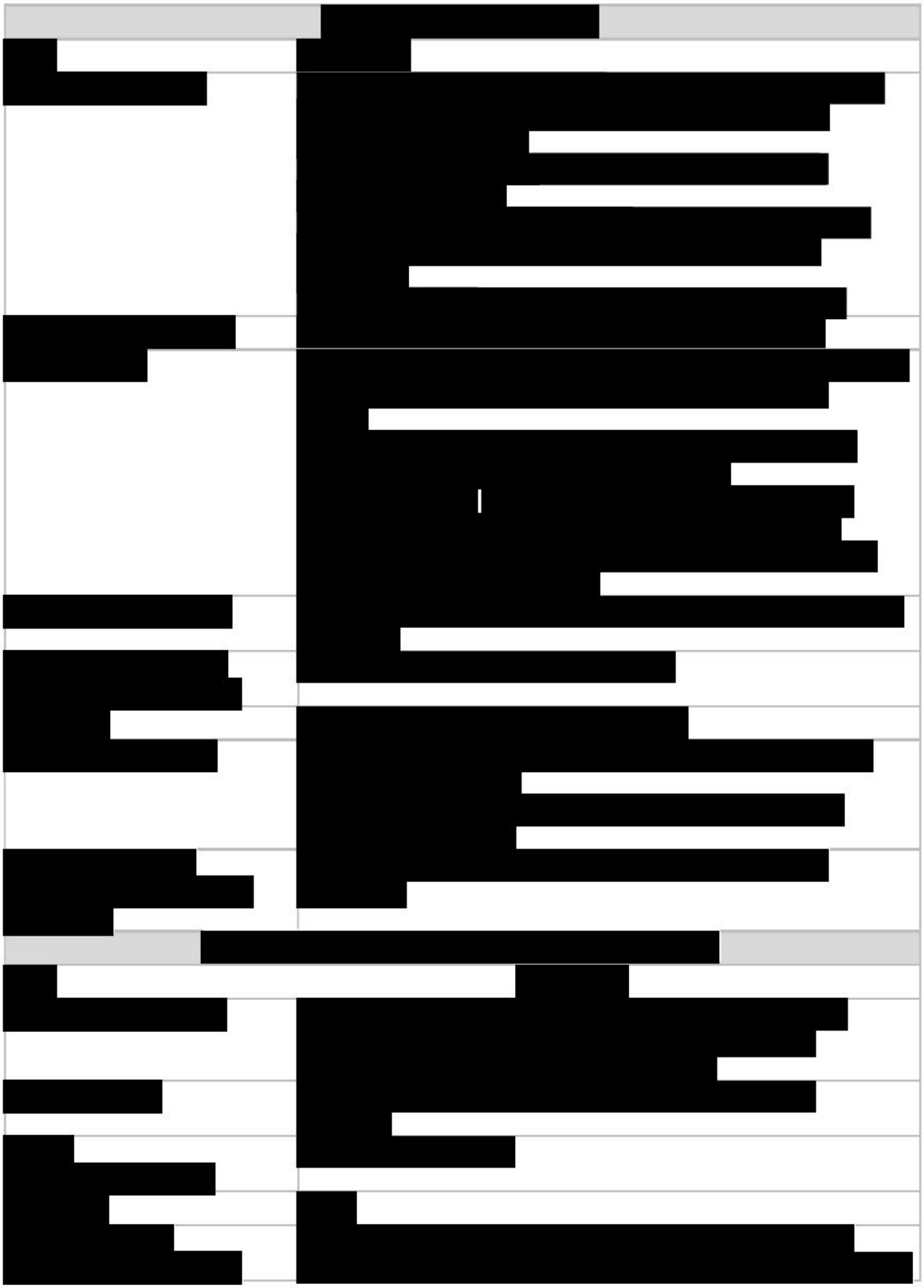
12 REFERENCES

[redacted]

Appendix 1: Schedule of Visits and Measurements



Appendix 2: Prohibited Medications List



Appendix 3: Examination Procedures, Tests, Equipment, and Techniques

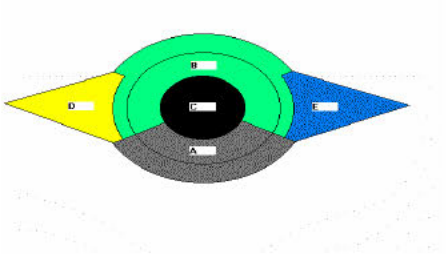
[redacted]

[redacted]

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

[redacted]

[redacted]



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

[redacted]

Appendix 4: Amendment Summary of Changes Table

Not applicable.

Appendix 5: Sponsor and [redacted] Approvals

Protocol Title: A Randomized, Double-Masked, Parallel Group, Vehicle-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease

Protocol Number: ADX-102-DED-032

Protocol Date: 19 Apr 2024

The clinical trial protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving the protocol.

[redacted]

[redacted]

[redacted]

Appendix 6: Investigator's Signature

Protocol Title: A Randomized, Double-Masked, Parallel Group, Vehicle-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease

Protocol Number: ADX-102-DED-032

Protocol Date: 19 Apr 2024

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] in confidence and, when the information is submitted to an Institutional Review Board (IRB) 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: Principal Investigator

Site:

Address:

Phone Number: