ALDEYRA THERAPEUTICS™

FINAL PROTOCOL REVIEW AND APPROVAL FORM

Protocol Number: ADX-102-DED-009. Product: reproxalap. [redacted]

Please check one:

- ☒ New Protocol
- ☐ Protocol Amendment
- ☐ Administrative Change

Protocol Title: A Multi-Center, Phase 2b, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled, Clinical Study to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% and 0.1%) Compared to Vehicle in Subjects with Dry Eye Disease

Version Number: 1.0

Version Date: 12 December 2017

[redacted]

Clinical Trial Protocol: ADX-102-DED-009

Protocol Title:	A Multi-Center, Phase 2b, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled, Clinical Study to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% and 0.1%) Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-009
Study Phase:	2b
Investigational Product Name:	Reproxalap Ophthalmic Solution (0.25% and 0.1%)
[redacted]	[redacted]
Indication:	Dry Eye Disease (DED)
Investigators:	Multi-Center
Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Ave. Lexington, MA 02421 USA
Contract Research Organization:	Ora. Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810 USA
[redacted]	[redacted]

	Date
Original Protocol:	12 December 2017
Amendment 1:	{revision date}

Confidentiality Statement

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SPONSOR PERSONNEL

[redacted]

ORA PERSONNEL

[redacted]

MEDICAL MONITOR

[redacted]

SYNOPSIS

Protocol Title:	A Multi-Center, Phase 2b, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled, Clinical Study to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% and 0.1%) Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-009
Investigational Product:	1) Reproxalap Ophthalmic Solution (0.25%) 2) Reproxalap Ophthalmic Solution (0.1%) 3) Vehicle Ophthalmic Solution
Study Phase:	2b
Objective(s):	To evaluate the efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.1%) on baseline to weeks 2, 4, 8 and 12 change score [redacted] To evaluate effect sizes for efficacy endpoints of Reproxalap Ophthalmic Solutions (0.25% and 0.1%) vs vehicle for the treatment of the signs and symptoms of dry eye disease to confirm the endpoint selection and sample size for Phase 3 studies with ADX-102. To evaluate the safety and tolerability of Reproxalap Ophthalmic Solutions (0.25% and 0.1%) to vehicle [redacted]
Overall Study Design:	
Structure:	Multi-center, double-masked, randomized study
Duration:	An individual subject's participation is estimated to be approximately 14 weeks (98 days).
Controls:	Vehicle Ophthalmic Solution
Dosage/Dose Regimen/ Instillation/Application/Use:	Screening: Between Visits 1 and 2, all subjects will receive 14 consecutive days (± 2) of Run-in (vehicle) ocular drops self–administered QID in both eyes.

	Treatment: During the 12 week (84 ± 3 days) treatment period, Reproxalap Ophthalmic Solution at concentrations of 0.1%, 0.25% or vehicle ophthalmic solution will be administered QID by bilateral topical ocular dosing. Subjects will be randomized to one of three treatment groups (1:1:1) to receive study drug after the Post–CAE® assessments at Visit 2.
Summary of Visit Schedule:	6 visits over the course of approximately 14 weeks • Visit 1 = Day -14 ± 2, CAE® Screening • Visit 2 = Day 1, CAE® Confirmation/ Baseline • Visit 3 = Day 15 ± 2, 2-Week Follow-Up • Visit 4 = Day 29 ± 2, 4-Week Follow-Up • Visit 5 = Day 57 ± 3, 8-Week Follow-Up • Visit 6 = Day 85 ± 3, 12-Week CAE® Follow-Up & Study Exit
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, double-masked study.
Study Population Characteristics:	
Number of Subjects:	Approximately 750 subjects will be screened to enroll approximately 300 subjects (100 per treatment group).
Condition/Disease:	Dry Eye Disease (DED)

Inclusion Criteria:	**Subjects must:** 1. Be at least 18 years of age of either gender and any race; 2. Provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form; 3. Have a reported history of dry eye for at least 6 months prior to Visit 1; 4. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; 5. [redacted] 6. Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm at Visit 1 and Visit 2; 7. [redacted] 8. Have a corneal fluorescein staining score [redacted] in at least one region (e.g. inferior, superior, or central) at Visit 1 and Visit 2 Pre-CAE®; 9. [redacted] [redacted] 11. Demonstrate a response to the CAE® at Visits 1 and 2 as defined by: A. Having at least a [redacted] increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure; B. Reporting an Ocular Discomfort score

	[redacted] 12 [redacted]
Exclusion Criteria:	**Subjects must not:** 1. Have any 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. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1; 3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study; 4. Have used any eye drops within 2 hours of Visit 1; 5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months; 6. Have used cyclosporine 0.05% or lifitigrast 5.0% ophthalmic solution within 90 days of Visit 1; 7. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1; 8. Be using or anticipate using temporary punctal

	plugs during the study that have not been stable within 30 days of Visit 1; 9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); 10. Have 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; 11. Be a woman who is pregnant, nursing, or planning a pregnancy; 12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (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. Be a man or woman of childbearing potential who is not using 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 study; 14. Have a known allergy and/or sensitivity to the

	test article or its components; 15. Have 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. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; 17. Have previously used reproxalap ophthalmic solution; 18. [redacted] 19. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.
Study Formulations and Formulation Numbers:	0.25% Reproxalap Ophthalmic Solution 0.1% Reproxalap Ophthalmic Solution Vehicle Ophthalmic Solution
Evaluation Criteria:	
Efficacy Measures and Endpoints:	[redacted] • Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire [redacted]

	[redacted]
Safety Measures:	• Visual acuity • Slit-lamp evaluation • Adverse event query • Intraocular Pressure (IOP) • Dilated fundoscopy

General Statistical Methods and Types of Analyses

Sample Size

- [redacted]

Efficacy Analysis

- Evaluate baseline to weeks 2, 4, 8 and 12 change scores with reproxalap on DED
- [redacted]
- [redacted]

Summary of Known and Potential Risks and Benefits to Human Subjects

Refer to Investigator's Brochure.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
API	active pharmaceutical ingredient
BCVA	best-corrected visual acuity
CAE	controlled adverse environment
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
CPT	Current Procedural Terminology
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CV	coefficient of variation
DED	dry eye disease
DHHS	Department of Health and Human Services
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IND	investigational new drug application
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
ITT	intent to treat
KCS	keratoconjunctivitis sicca
LASIK	laser in situ keratomileusis
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant

ND	not done
NDA	new drug application
NF	national formulary
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
OS	left eye
[redacted]	[redacted]
OU	both eyes
OTC	over the counter
PE	polyethylene
PHI	protected health information
PO	by mouth
PP	per protocol
PRN	as needed
QD	once daily
QID	Four times daily
QS	as much as will suffice
ROPI	Report of Prior Investigations
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
[redacted]	[redacted]
SOP	standard operating procedure
TF	tear film
[redacted]	[redacted]
T_{max}	time of maximum concentration
USP	United States Pharmacopeia
VA	visual acuity
w/v	weight per unit volume

1 INTRODUCTION

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

2 Clinical Studies of Reproxalap Ophthalmic Solution

Reproxalap topical ocular solution is being developed for ocular inflammation. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]				

NA = not applicable; QID = 4-times daily

[redacted]

Table 2. Topical Ocular Reproxalap Clinical Trial Outcomes

Clinical Trial	Indication	Summary Outcome
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

2.1 Minimization of Risk

[redacted]

3 STUDY OBJECTIVES

The study objectives are as stated below:

- To evaluate the efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.1%) on baseline to weeks 2, 4, 8 and 12 change scores [redacted]
- To evaluate effect sizes for efficacy endpoints of Reproxalap Ophthalmic Solutions (0.25% and 0.1%) versus vehicle for the treatment of the signs and symptoms of dry eye disease to confirm the endpoint selection and sample size for Phase 3 studies with ADX-102.
- To evaluate the safety and tolerability of Reproxalap Ophthalmic Solutions (0.25% and 0.1%) to vehicle [redacted]

4 CLINICAL HYPOTHESES

The clinical hypotheses for this study are that 0.10% and/or 0.25% Reproxalap Ophthalmic Solution is superior to vehicle [redacted]

5 OVERALL STUDY DESIGN

This is a Phase 2b, multicenter, randomized, double–masked, vehicle-controlled, parallel-group design with block enrollment. Subjects will be randomized to one of the following treatment groups at Visit 2 and will be instructed to follow a QID-dosing regimen:

- Reproxalap 0.1% Ophthalmic Solution (N~100)
- Reproxalap 0.25% Ophthalmic Solution (N~100)
- Vehicle of Reproxalap Ophthalmic Solution (N~100)

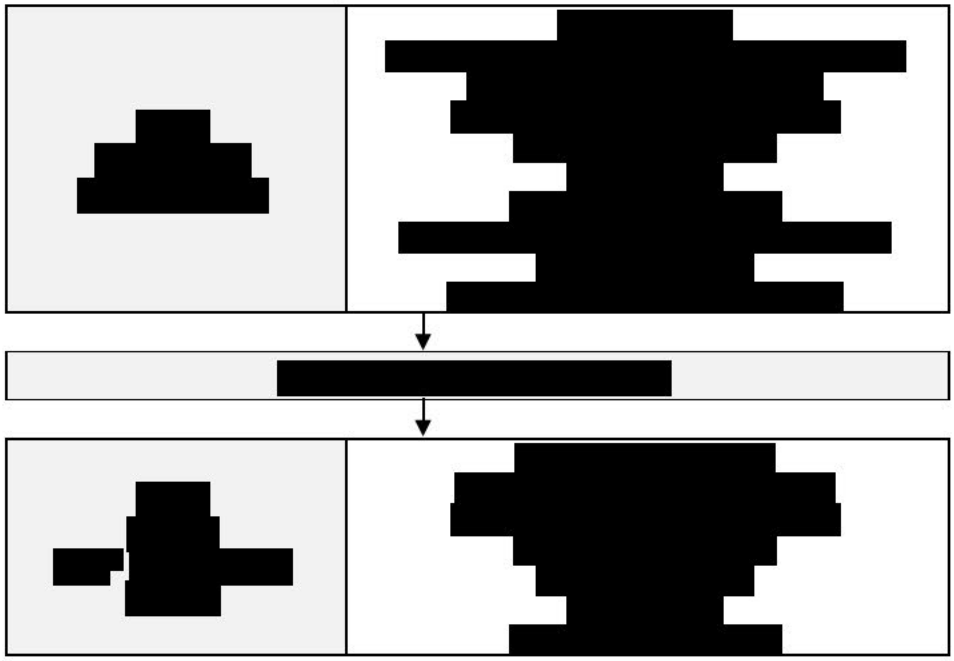
This study is multicenter, randomized, double–masked, vehicle–controlled, parallel-group design with block enrollment. Approximately 300 subjects will be randomly assigned to one of the three treatment groups (1:1:1) to receive either Reproxalap Ophthalmic Solution (0.1%, 0.25%) or vehicle solution as topical ophthalmic drops administered bilaterally QID. Subjects, Sponsor, CRO and site personnel will be masked to treatment assignment.

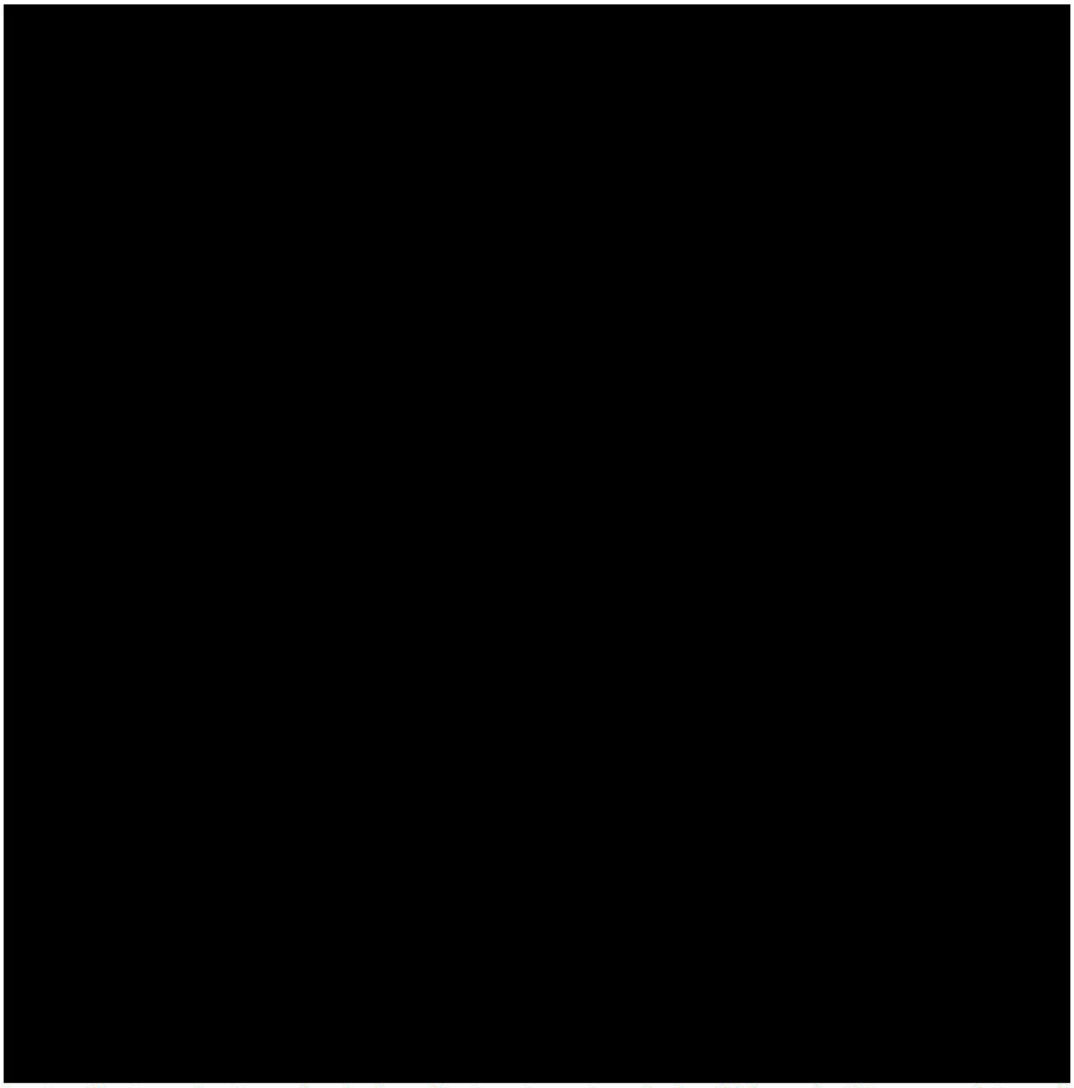
During the screening period, two 90-minute exposures to the CAE® will be conducted to ascertain eligibility to enter the study. Those who qualify will be randomized to receive study drug in a double-masked fashion for 84 days. Subjects will self-administer drops four times daily and will complete daily diary assessments as instructed.

At Visit 6 (Day 85), CAE® exposure will occur, with pre-CAE®, during CAE® (symptoms only) and post-CAE® assessments of ocular signs and symptoms. At Visits 3, 4 and 5, no CAE® exposure will occur [redacted]

The total number of expected participants, including screen failures, is approximately 750 subjects.

A [redacted]





Subjects who terminate early during the treatment period will be asked to complete safety assessments prior to commencement of any alternative dry eye therapy (if at all possible). Subjects who are terminated early from the study will not be replaced.

6 STUDY POPULATION

6.1 Number of Subjects (approximate)

It is estimated that approximately 750 subjects will be screened to enroll approximately 300 randomized subjects (100 in each group). Subjects will be randomized in a 1:1:1 ratio of Reproxalap Ophthalmic Solution (0.1%) to Reproxalap Ophthalmic Solution (0.25%) to vehicle ophthalmic solution.

6.2 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.

6.3 Inclusion Criteria

Each subject must:

1. Be at least 18 years of age of either gender and any race;
2. Provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form;
3. Have a reported history of dry eye for at least 6 months prior to Visit 1;
4. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1;
5. Report a score of [redacted]
6. Have a Schirmer's Test score of [redacted] Visit 1 and Visit 2;
7. Have a tear [redacted] at Visit 1 and Visit 2 [redacted]
8. Have a corneal fluorescein staining score [redacted] at Visit 1 and Visit 2 [redacted];
9. Have a sum corneal fluorescein staining score [redacted], at Visit 1 and Visit 2 [redacted];
10. Have a total lissamine green conjunctival [redacted] at Visit 1 and Visit 2 [redacted]
11. Demonstrate a response to the [redacted] at Visits 1 and 2 as defined by:
    A. Having at least [redacted] fluorescein staining in the inferior region in at least one eye following [redacted] exposure;
    B. Reporting an Ocular Discomfort [redacted] 2 or more consecutive time points in at least one eye during [redacted]

6.4 Exclusion Criteria

Each subject may not:

1. Have any 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. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;
3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study;
4. Have used any eye drops within 2 hours of Visit 1;
5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months;
6. Have used cyclosporine 0.05% or lifitigrast 5.0% ophthalmic solution within 90 days of Visit 1;
7. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1;
8. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;
9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study);
10. Have 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;
11. Be a woman who is pregnant, nursing, or planning a pregnancy;
12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (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. Be a man or woman of childbearing potential who is not using 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 study;
14. Have a known allergy and/or sensitivity to the test article or its components;
15. Have 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. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;

17. Have previously used reproxalap ophthalmic solution;
18. Be currently using 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;
19. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

6.5 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 9.6.2).

7 STUDY PARAMETERS

7.1 Efficacy Measures and Endpoints

7.1.1 Efficacy Measure(s)

[redacted]

[redacted] Questionnaire

- Ocular Surface Disease Index (OSDI)©

[redacted]

7.1.2 Efficacy Endpoint(s)

The efficacy endpoints are changes from baseline at weeks 2, 4, 8 and 12 for each efficacy measure, where available. Endpoints will be calculated pre-CAE and, where available post-CAE and as pre- to post-CAE changes.

7.1.3 Criteria for Effectiveness

Success would be demonstrating statistically significant ($p<0.05$) effects on at least one DED sign or at least one DED symptom at week 12

7.2 Safety Measures

- Visual acuity (ETDRS);
- Slit-lamp biomicroscopy;
- Adverse event query;
- Dilated Fundoscopy;
- Intraocular Pressure;

8 STUDY MATERIALS

8.1 Study Treatment(s)

8.1.1 Study Treatment(s)/ Formulation(s)

- Reproxalap Ophthalmic Solution (0.25%)
- Reproxalap Ophthalmic Solution (0.10%)
- Vehicle Ophthalmic Solution

8.1.2 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s).

Topical ophthalmic dosing is the optimal route of administration for dry eye treatments. The dosage and dosage regimen was selected based on nonclinical and clinical studies described in Section 2. [redacted]

8.1.3 Instructions for Use and Administration

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

[redacted]

8.2 Other Study Supplies

[redacted]

9 STUDY METHODS AND PROCEDURES

9.1 Subject Entry Procedures

9.1.1 Overview

Subjects as defined by the criteria in sections 6.2, 6.3, and 6.4 will be considered for entry into this study.

9.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or 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. The informed consent form must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board (IRB).

9.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the exclusion criteria (Section 6.4).

9.1.4 Procedures for Final Study Entry

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

9.1.5 Methods for Assignment to Treatment Groups:

Before the initiation of study run-in at Visit 1, each subject who provides written and informed consent will be assigned to a screening number. All screening numbers will be assingned in strict numerical sequence at a site and no numbers will skipped or omitted. Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1 and Visit 2 will be assigned a randomization number at the end of Visit 2. The Interactive Web Response System (IWRS) will be used to assign all randomization numbers.

Randomization and kit numbers will be assigned automatically to each subject as they are entered into the IWRS.

The site staff will dispense kit(s) required until the next visit. Both the randomization number and the dispensed study drug kit number(s) will be recorded on the subject's

source document and eCRF. The sponsor, investigators, and study staff will be masked during the randomization process and throughout the study.

9.2 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 medical device study is not permitted.

9.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 6.4).

9.2.2 Escape Medications

No escape medications are required for this study.

9.2.3 Special Diet or Activities

No special diets or activities are required for this study.

9.3 Examination Procedures

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

Procedures listed below should be performed in the given order. See Appendix 2 for details on methodologies and grading systems.

9.3.2 Visit 1: Day –14 ± 2 – CAE® Screening

All subjects will undergo the following screening assessments:

[redacted]

- Informed Consent/HIPAA
- Demographic Data and Medical/Medication/Ocular History
- Review of Inclusion/Exclusion Criteria
- Urine Pregnancy Test (for females of childbearing potential): Women of childbearing potential must have a negative urine pregnancy test to continue in the study
- [redacted]

[redacted]

[redacted]

- [redacted]

Post–CAE®

[redacted]

- AE Query
- IOP
- Dilated Fundoscopy
- Review of Inclusion/Exclusion Criteria
- Run-in Instillation at the Study Site: All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria at the end of Visit 1 will receive run-in drops for dosing. Qualified subjects will self-administer their initial run-in dose bilaterally at the study site under supervision of a trained technician.
- Run-in (Vehicle) and Diary Dispensation: Prior to discharge from the study site on Day –14, subjects will be dispensed sufficient Run-in supply to last until Visit 2 and will be educated in diary recording and self–administration of vehicle run-in. Subjects will be instructed to self–administer one drop QID in each eye until Visit 2. Subjects will be instructed NOT to instill run-in on the morning of their next scheduled study visit (Visit 2).

- AE Query
- Subjects will be scheduled for Visit 2.

9.3.3 Visit 2: Day 1 – [redacted]

[redacted]

- [redacted] Diary/Run-in Collection
- Review of Inclusion/Exclusion Criteria
- Medical/medication history update
- AE query
- [redacted]
- [redacted]
- [redacted] Que[redacted]

[redacted]

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

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

- Review of Inclusion/Exclusion Criteria
- Randomization
- Study Drug Instillation at the Study Site: All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria at the end of Visit 2 will be randomized to one of three treatment groups utilizing the IWRS system. Randomized subjects will self-administer their initial study drug dose bilaterally at the study site under supervision of a trained technician.
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 2 (Day 1), randomized subjects will be educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 3 and will be instructed NOT to self–administer study drug on the morning of their next scheduled study visit (Visit 3).
- AE Query
- Subjects will be scheduled for Visit 3.

9.3.4 Visit 3 (Day 15 ±2)

- Study Drug Diary/Study Drug Collection
- Medical/medication history update
- AE query
- [redacted]

[redacted] Utilizing an ETDRS Chart

[redacted]

- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 3, subjects will be assigned a new study drug kit via the IWRS and will also be re-dispensed the remaining unused ampules from their previous kit for at-home dosing up to Visit 4. Subjects will again be educated in study drug diary recording and self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 4)

- AE Query
- Subjects will be scheduled for Visit 4.

9.3.5 Visit 4: Day 29 ± 2

- Study Drug Diary/Study Drug Collection
- Medical/medication history update;
- AE query;
- [redacted]

[redacted]

- Study Drug Diary/Study Drug Re-dispensation: Prior to discharge from the study site on Visit 4, subjects will be assigned two new study drug kits via the IWRS and will also be re-dispensed the remaining unused ampules from their previous kits for at-home dosing up to Visit 5. Subjects will again be educated in study drug diary recording and self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 5)
- AE Query
- Subjects will be scheduled for Visit 5.

9.3.6 Visit 5: Day 57 ± 3

- Study Drug Diary/Study Drug Collection
- Medical/medication history update
- AE query
- [redacted]

[redacted]

- [redacted]

[redacted]

- Study Drug Diary/Study Drug Re-dispensation: Prior to discharge from the study site on Visit 5, subjects will be assigned a new study drug kit via the IWRS and will also be re-dispensed the remaining unused ampules from their previous kits for at-home dosing up to Visit 6. Subjects will again be educated in study drug diary recording and self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 6)
- AE Query
- Subjects will be scheduled for Visit 6.

9.3.7 Visit 6: Day 85 ± 3

[redacted]

[redacted] Drug Diary/Study Drug Collection

- Medical/medication history update
- AE query
- Urine Pregnancy Test (for females of childbearing potential)
- [redacted]

[redacted]e

[redacted]

- [redacted]

[redacted] Utilizing an ETDRS Chart

[redacted]

[redacted]

- Intraocular Pressure
- Dilated fundoscopy
- AE Query
- Study Exit

9.4 Schedule of Visits, Measurements and Dosing

9.4.1 Scheduled Visits

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

9.4.2 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:

- Slit-lamp Biomicroscopy
- Visual Acuity
- Intraocular Pressure
- Urine Pregnancy Test
- Dilated Fundoscopy
- Assessment of Adverse Events

- Assessment of concomitant medications and/or treatments
- Any other assessments needed in the judgment of the investigator.

9.5 Compliance with Protocol

Subjects will be instructed on proper use of the subject daily diary and proper instillation and storage of study drug at the end of Visits 1, 2, 3, 4 and 5, and given written instructions. [redacted]

9.6 Subject Disposition

9.6.1 Completed Subjects

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

9.6.2 Discontinued Subjects

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

- subject request/withdrawal
- AEs
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- sponsor termination of study
- other

Note: In addition, any subject may be discontinued for any sound medical reason.

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora and/or sponsor and will be clearly documented on the eCRF.

9.7 Study Termination

The study may be stopped at any time by the investigator, the sponsor, and/or Ora with appropriate notification.

9.8 Study Duration

An individual subject's participation will involve 6 visits over approximately a 14-week (~98 days) period (84 days of treatment and 14 days pre-screening).

9.9 Monitoring and Quality Assurance

During the course of the study an Ora monitor, or designee, will make routine site visits to review protocol compliance, assess IP accountability, 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, quality assurance 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.

10 ADVERSE EVENTS

10.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. 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.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, and relationship to IP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning. Exacerbation of conditions related to the signs and symptoms of Dry Eye will not be reported as an AE.

10.1.1 Severity

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

10.1.2 Relationship to Investigational Product

The Investigator must assess whether they consider an AE to be drug-related. In assessing this relationship, the Investigator must use information about the conditions/concurrent medication, and chronology of the event relative to drug administration. The following definitions will be used:

- ***Definitely Related***
- ***Probably Related***
- ***Possibly Related***
- ***Unlikely to be related***
- ***Not Related***

10.1.3 Expectedness

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

- ***Unexpected:*** An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- ***Expected:*** An AE that is listed in the IB at the specificity and severity that has been observed.
- ***Not applicable:*** An AE unrelated to the IP.

AE events that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

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

10.2 Serious Adverse Events

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

- Death;
- A life-threatening AE;

Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE 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 (SAE) 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health

authorities and recorded on the appropriate CRF. Adverse Events will be collected after the signing of the Informed Consent.

10.3.1 Reporting a Suspected Unexpected Adverse Reaction

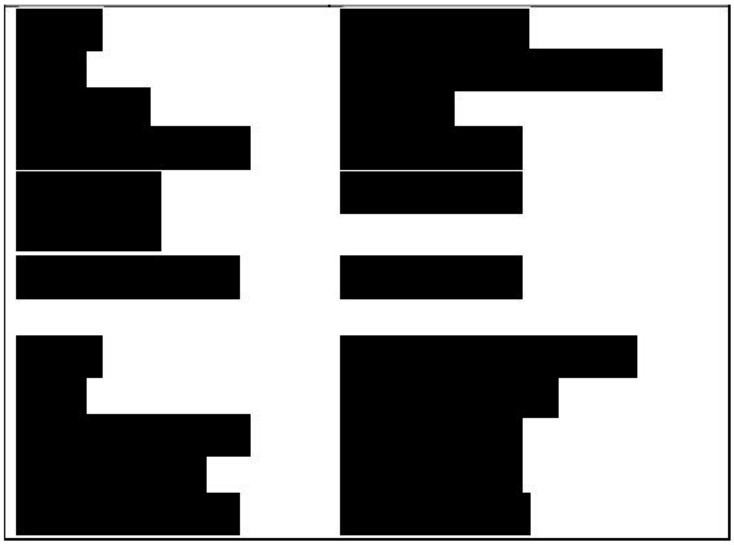
All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

10.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate CRFs. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the CRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify Ora and the sponsor immediately; 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 Ora and the 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 IP; and inform the IRB of the SAE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:



10.4 Procedures for Unmasking (if applicable)

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 group has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be

notified before unmasking study drug. Ora and/or the study sponsor must be informed immediately about any unmasking event.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact Ora and/or the medical monitor prior to unmasking the identity of the IP, if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify Aldeyra and jointly will determine if the unmasking request should be granted. They may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject 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 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.

Unmasked subjects will be discontinued from the study.

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

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to Ora within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

11 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

11.1 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 study. 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 the investigational product. Subjects in the Safety population will be analyzed as treated.

The statistical analysis of safety data will be performed for the safety population. The analysis of efficacy data will be performed for the ITT population and on the PP population as sensitivity analyses.

11.2 Statistical Hypotheses

11.3 Sample Size

11.4 Statistical Analysis

11.4.1 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 group. 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 WHO Drug dictionaries, as appropriate.

[redacted]

All analyses will be 2-sided at a significance level of 0.05. 80% and 95% confidence intervals will be provided where appropriate.

11.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the study eye, or the "worst eye," as defined by the following:

[redacted]

[redacted] Data

Analyses will be performed on the ITT population with the Last Observation Carried Forward (LOCF) imputation method for missing values. Efficacy analyses may also be conducted using the ITT population with observed data only (i.e., without LOCF) and the PP population to assess sensitivity as detailed further in the statistical analysis plan (SAP).

11.4.4 Multiplicity Consideration

As this is a Phase 2b study, there will be no multiplicity adjustments for the two active treatments or for the multiple endpoints.

11.4.5 Efficacy Analyses

[redacted]

11.4.6 Safety Variables

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature 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; by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class and preferred term for treatment-related TEAEs; and by system organ class, preferred term, and study day of onset. Separate summaries will be performed for ocular and non-ocular AEs.

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye, and fellow eye will be summarized separately.

11.4.7 Interim Analyses

There will be no interim analyses in this study.

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

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonisation (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 IP in the countries involved will be adhered to.

12.1 Protection of Human Subjects

12.1.1 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 and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

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.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by Ora and/or sponsor and provided in writing by Ora and/or sponsor prior to the consent process.

12.1.2 Institutional Review Board (IRB) Approval

This study 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 study and re-approval at least annually.

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

12.2 Ethical Conduct of the Study

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

12.3 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 is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the sponsor, the IRB/IEC approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the 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 IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

12.4 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 CRFs serves as the investigator's record of a subject's study-related data.

12.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all IP, and copies of CRFs 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 IP. 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.

12.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

12.5.1 Labeling/Packaging

Investigational drug will be packaged and labeled into clinical kits.

[redacted]

[redacted]

12.5.2 Storage of Investigational Product

[redacted]

12.5.3 Accountability of Investigational Product

The IP 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 IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP dispensed to subjects, amount of IP returned to the investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the IP.

12.5.4 Return or Disposal of Investigational Product

All IP will be returned to the sponsor or their designee or destroyed at the study site. The return or disposal of IP will be specified in writing.

12.6 Recording of Data on Source Documents and Case Reports Forms (CRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's CRF, 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.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system. Data will not be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

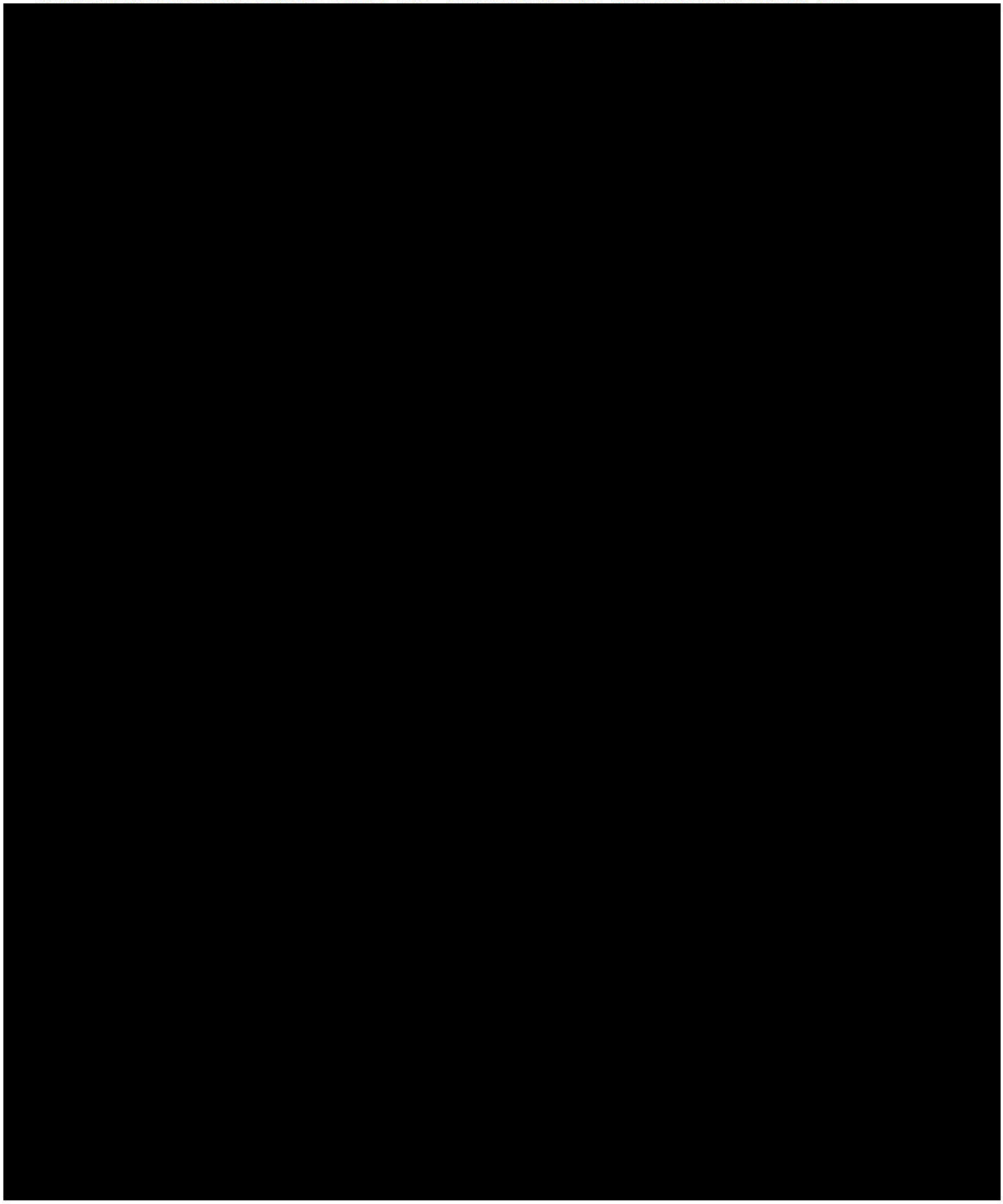
12.7 Publications

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

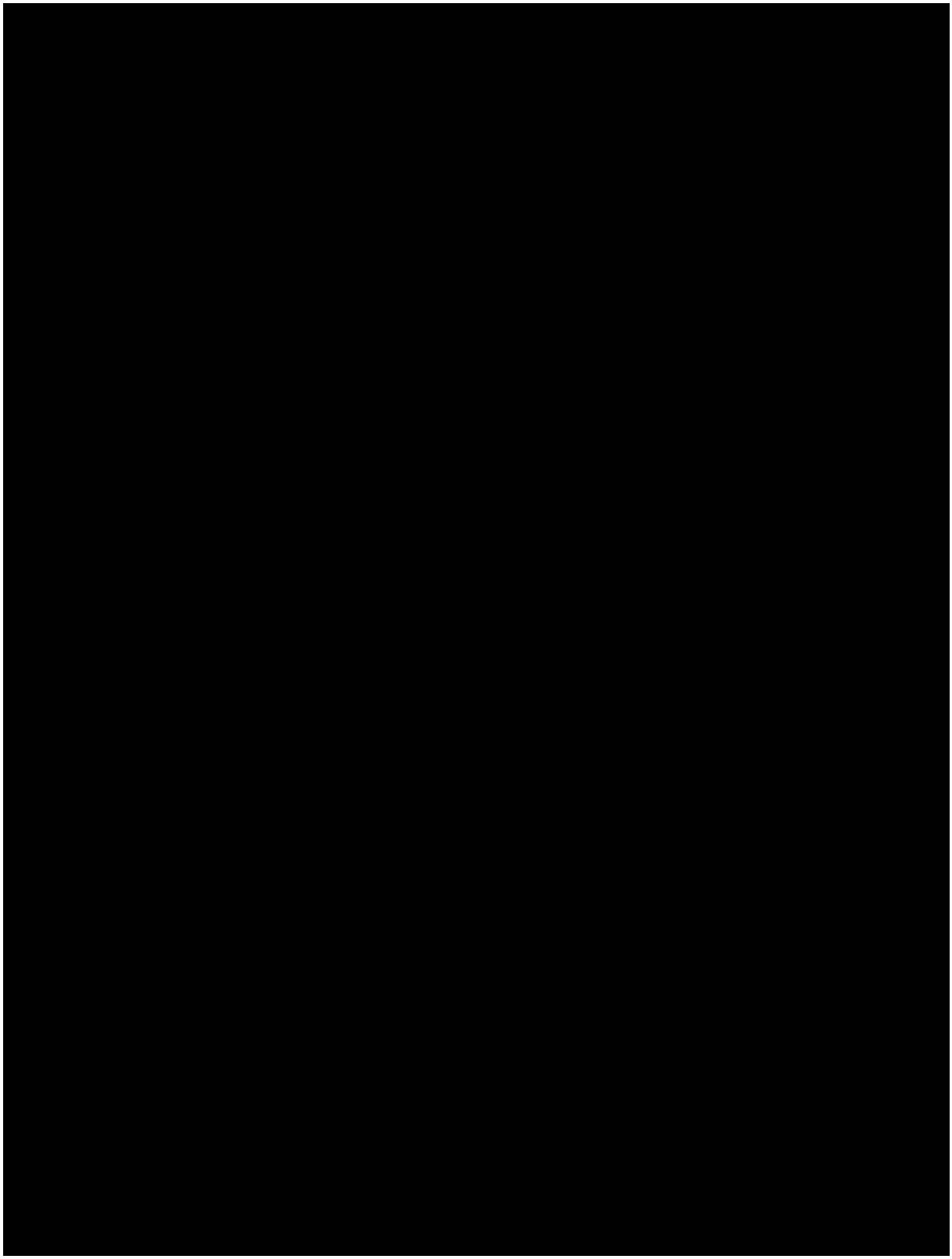
13 REFERENCES

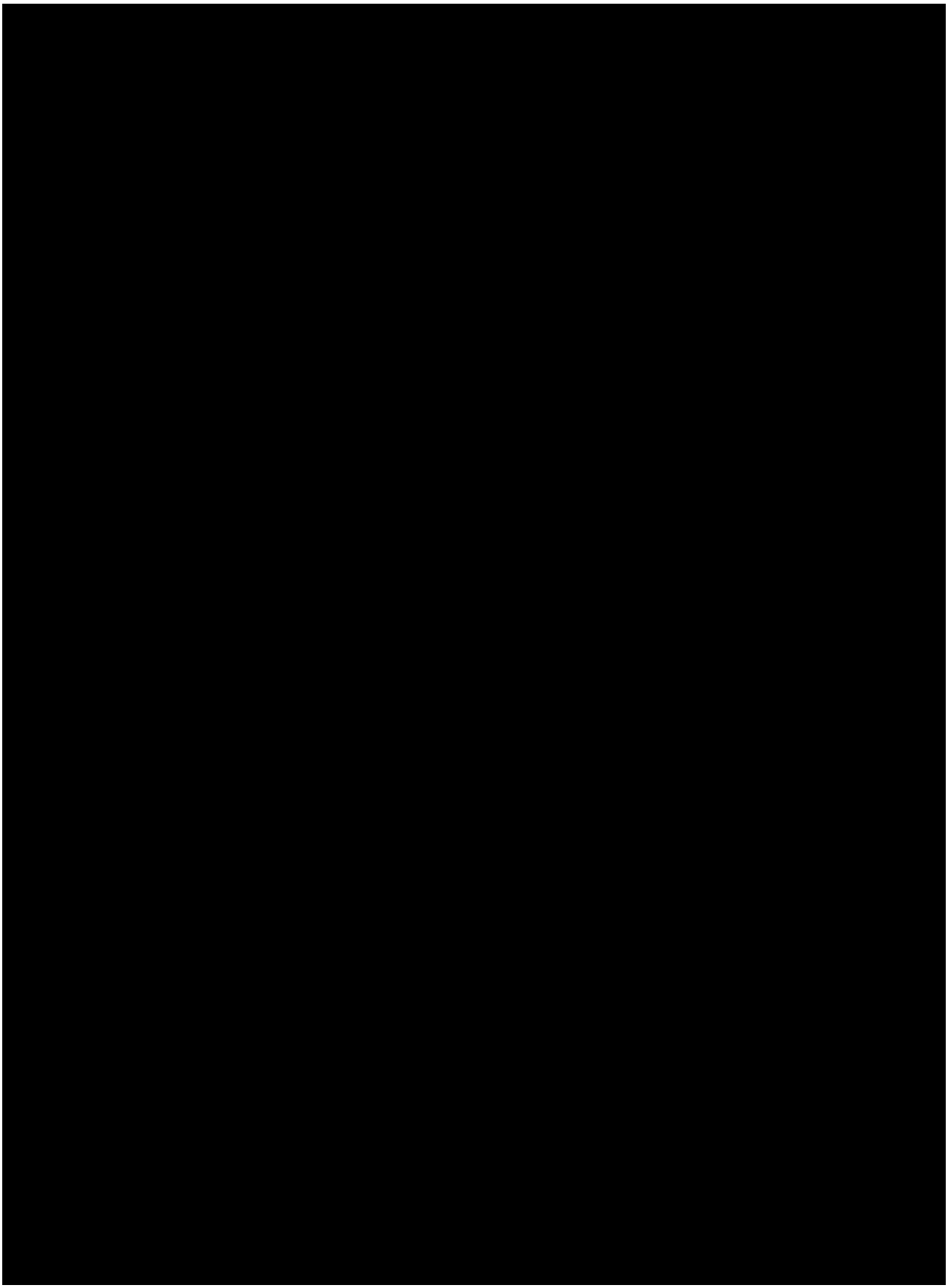
14 APPENDICES

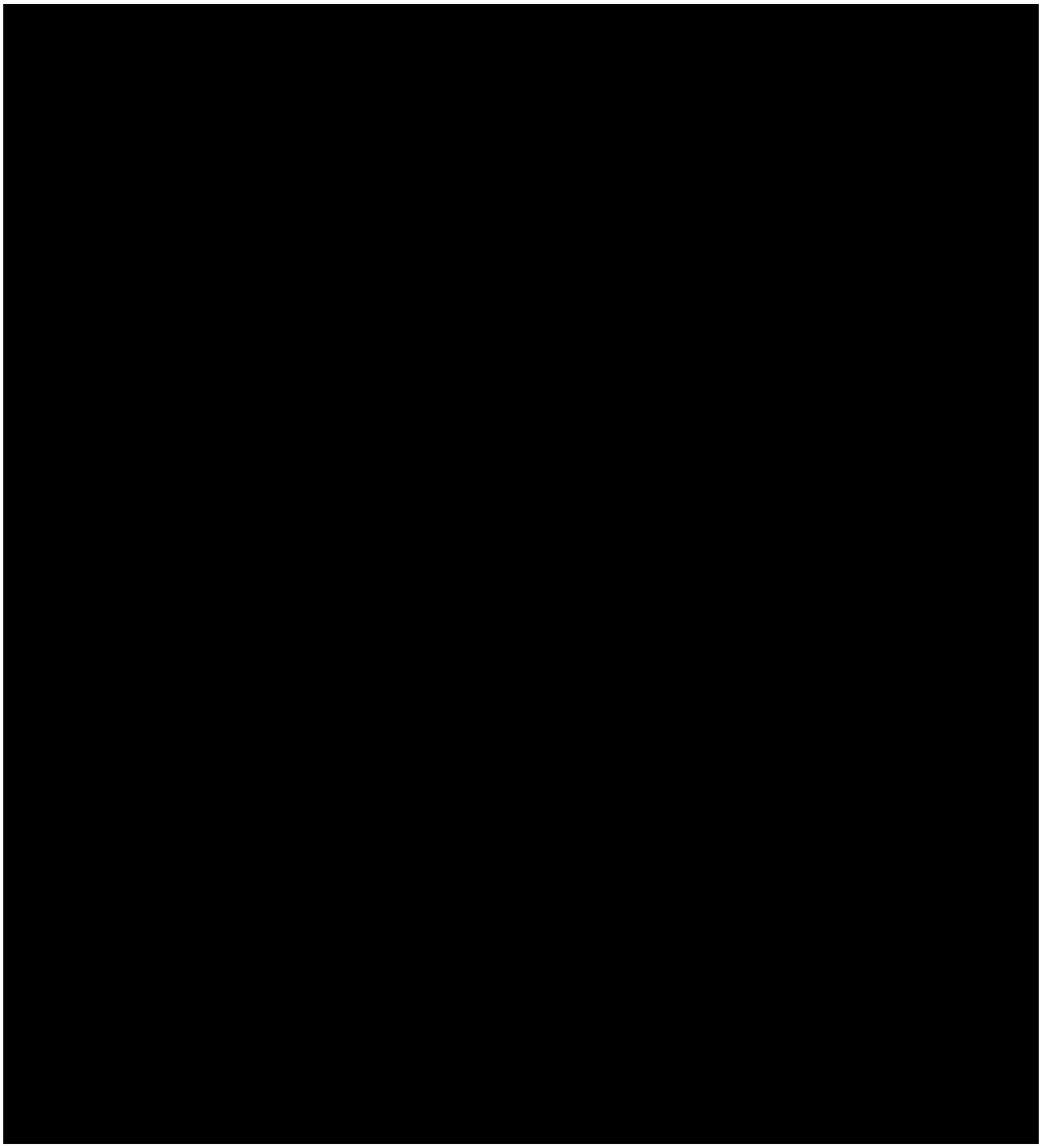
APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS



APPENDIX 2: EXAMINATION PROCEDURES, TESTS, & EVALUATIONS







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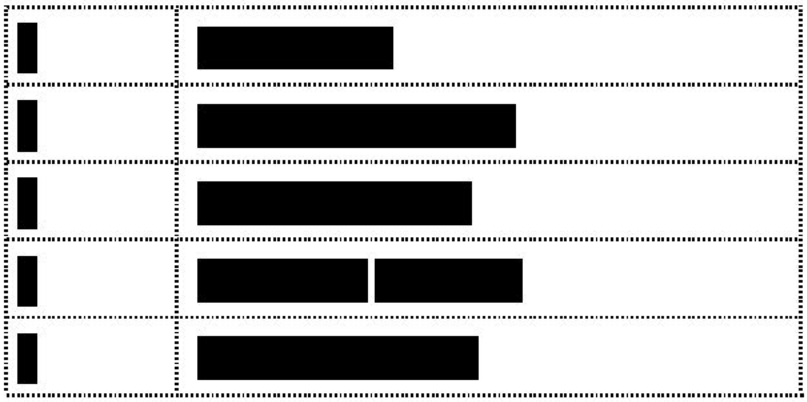

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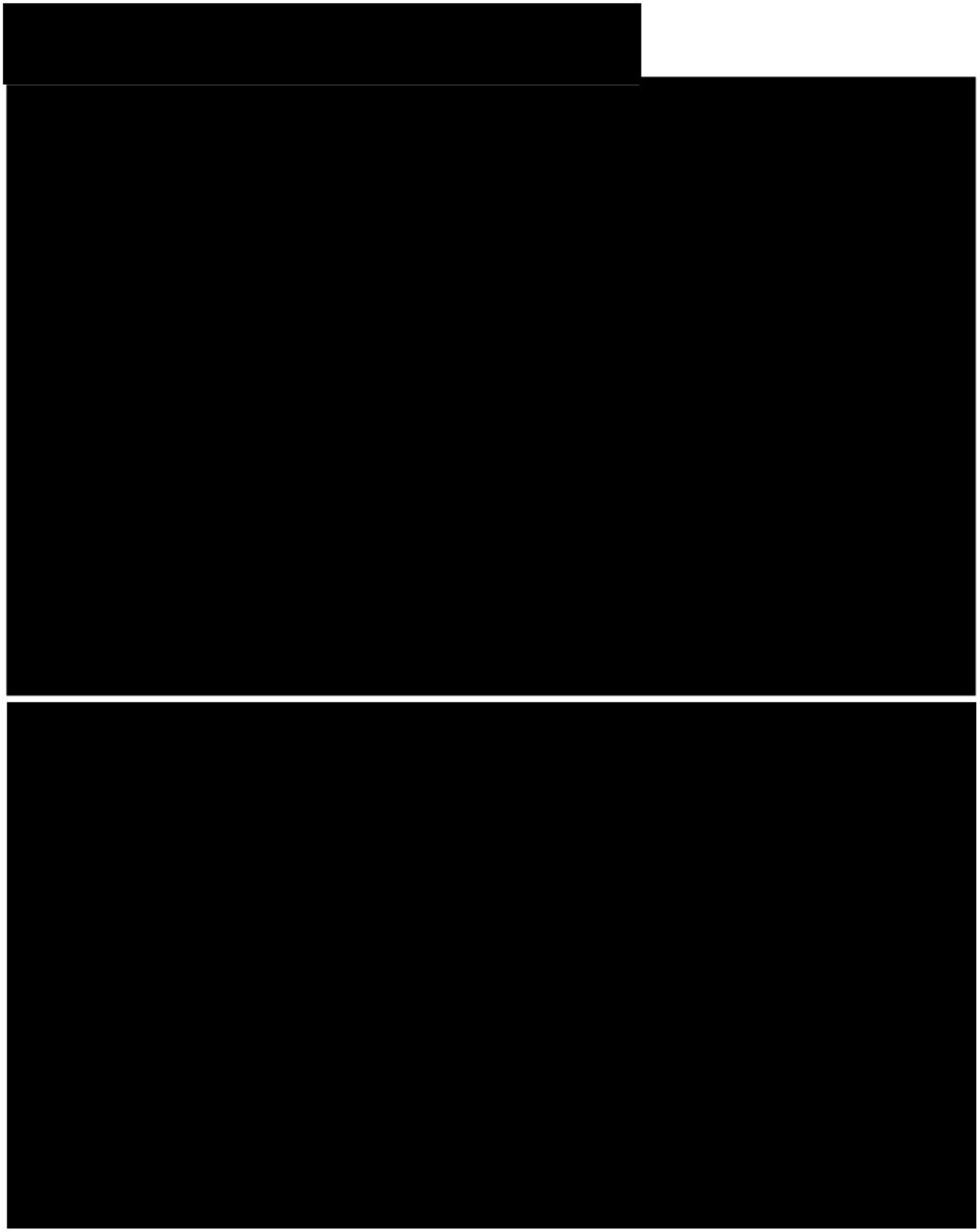

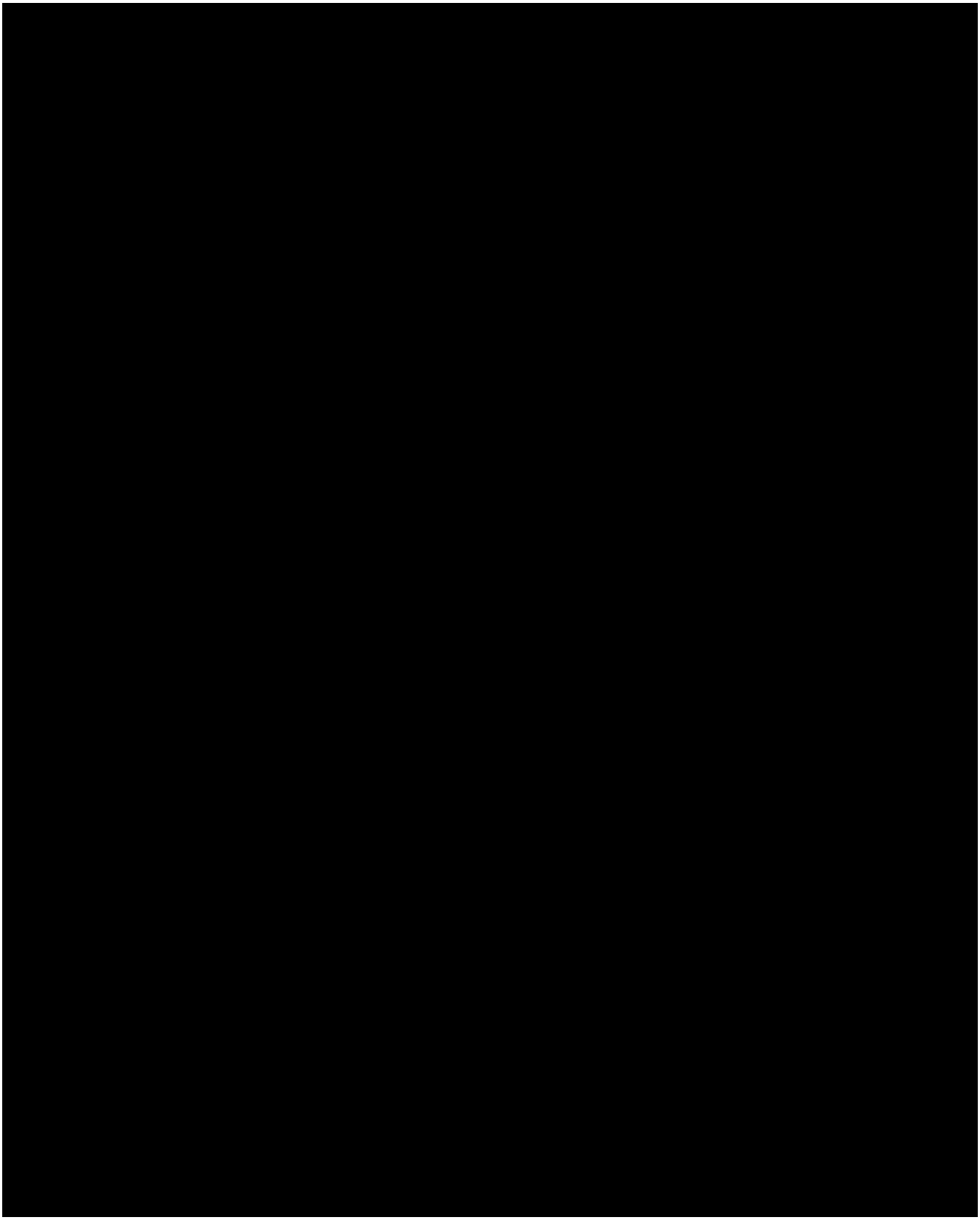

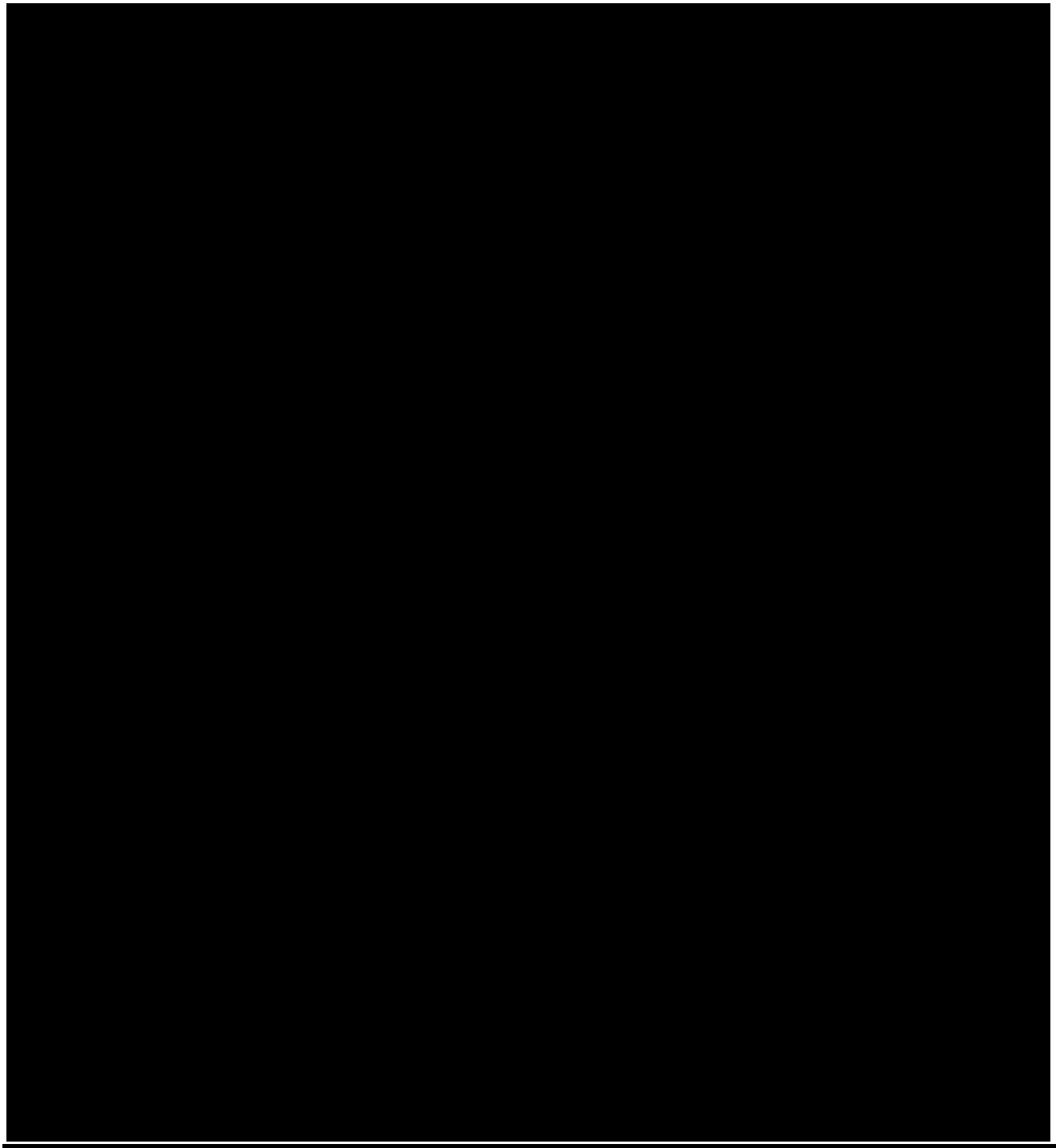

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APPENDIX 3: PROTOCOL AMENDMENT SUMMARY

Not Applicable.

APPENDIX 4: SPONSOR AND ORA APPROVALS

Protocol Title: A Multi-Center, Phase 2b, Randomized, Double Masked, Parallel-Group, Vehicle-Controlled, Clinical Study to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% and 0.1%) Compared to Vehicle in Subjects with Dry Eye Disease

Protocol Number: ADX-102-DED-009

Final Date: 12 December 2017

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.

APPENDIX 5: INVESTIGATOR'S SIGNATURE

Protocol Title: A Multi-Center, Phase 2b, Randomized, Double Masked, Parallel-Group, Vehicle-Controlled, Clinical Study to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% and 0.1%) Compared to Vehicle in Subjects with Dry Eye Disease

Protocol Number: ADX-102-DED-009

Final Date: **12 December 2017**

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 Ora 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.