CLINICAL TRIAL PROTOCOL: ADX-102-AC-008

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis
Protocol Number:	ADX-102-AC-008
Name of Test Drug /Investigational Product:	Reproxalap Ophthalmic Solution (0.25% and 0.5%)
IND/IDE/PMA Number:	[redacted]
Indication Studied:	Acute allergic conjunctivitis
Development Phase:	3
Brief Description:	Multi-center, double-masked, randomized, parallel-group, vehicle-controlled, phase 3 CAC trial.
Name of Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Ave. Lexington, MA 02421 USA
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, Third Floor Andover, MA 01810 USA
IRB/IEC:	[redacted]
	Date
Original Protocol:	15 February 2018

Confidentiality Statement

This protocol contains confidential, proprietary information of Ora, Inc. and/or Aldeyra Therapeutics, Inc. Further dissemination, distribution or copying of this protocol or its contents is strictly prohibited.

SPONSOR (Aldeyra) PERSONNEL

Chief Medical Officer:	[redacted]

ORA PERSONNEL

Chief Medical Officer:	[redacted]
Department Vice President:	[redacted]
Project Lead:	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Sponsor: Aldeyra Therapeutics, Inc.

Name of Finished Product: Reproxalap Ophthalmic Solutions (0.25% and 0.5%)

Name of Active Ingredient: reproxalap

Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

Protocol Number: ADX-102-AC-008

Investigator: Multi-Center

Study Phase of Development: 3

Objectives:

To evaluate the safety and efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) compared to vehicle for the treatment of ocular itching associated with acute allergic conjunctivitis

Methodology:

Structure:

Multi-center, double-masked, randomized, parallel-group, vehicle-controlled, phase 3 clinical trial to evaluate the safety and efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) compared to vehicle for the treatment of ocular itching associated with acute allergic conjunctivitis

Duration: This trial consists of [redacted] over a period of approximately [redacted].

Screening Period: Screening will be [redacted].

Treatment Period: Treatment will begin at [redacted] after subjects are randomized. At this visit, subjects will receive an in-office dose of the treatment.

Summary of Visit Schedule:

- Screening Visit [redacted] Screening/Informed Consent/ Skin Test
- Visit [redacted] Titration CAC
- Visit 2 [redacted] Confirmation CAC
- Visit 3 [redacted] Enrollment, randomization, and test article administration [redacted]

Measures Taken to Reduce Bias:

Randomization will be used to avoid bias in the assignment of subjects to test article, to increase the likelihood that known and unknown subject attributes [redacted] are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. In addition, randomization will be [redacted] Finally, masked treatment will be used to reduce potential of bias during data

Sponsor: Aldeyra Therapeutics, Inc.
Name of Finished Product: Reproxalap Ophthalmic Solutions (0.25% and 0.5%)
Name of Active Ingredient: reproxalap
Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis
collection and evaluation of clinical endpoints.
Study Population Characteristics
Number of Subjects: Approximately [redacted] subjects will be screened in order to enroll [redacted]
Diagnosis: Acute allergic conjunctivitis
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 HIPAA form; 3) be willing and able to follow all instructions and attend all trial visits; 4) have a positive history of ocular allergies and a positive skin test reaction to a seasonal allergen [redacted] as confirmed by an allergic skin test at the Screening Visit or within the past 24 months; 5) be able and willing to avoid all disallowed medications for the appropriate washout period and during the trial (see exclusion 6); 6) be able and willing to discontinue wearing contact lenses [redacted]; 7) have a calculated visual acuity [redacted] as measured using an ETDRS chart; 8) agree to have urine pregnancy testing (for women considered capable of becoming pregnant, including all females who have experienced menarche and have not experienced menopause [as defined by amenorrhea for greater than 12 consecutive months] or have not undergone successful surgical sterilization [hysterectomy, bilateral tubal ligation, or bilateral oophorectomy]) performed at screening and exit visit; not be lactating; and agree to use a medically acceptable form of birth control[1] throughout the trial duration; 9) have a positive bilateral CAC reaction [redacted] instillation of the last titration of allergen [redacted] 10) have a positive bilateral CAC reaction [redacted] following the challenge [redacted]

[1]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
[redacted]

Sponsor: Aldeyra Therapeutics, Inc.

Name of Finished Product: Reproxalap Ophthalmic Solutions (0.25% and 0.5%)

Name of Active Ingredient: reproxalap

Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

Exclusion Criteria

Each subject may not:

1) have known contraindications or sensitivities to the use of the investigational product or any of its components;
2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters [redacted]
3) have had ocular surgical intervention [redacted] and/or a [redacted] or have ocular or systemic surgery planned [redacted]
4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
5) have the presence of an [redacted] at any visit;
6) use any of the following disallowed medications during the period indicated [redacted] and during the trial:

[redacted]

7) have any significant illness [redacted]

Sponsor: Aldeyra Therapeutics, Inc.

Name of Finished Product: Reproxalap Ophthalmic Solutions (0.25% and 0.5%)

Name of Active Ingredient: reproxalap

Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

[redacted] that, at the investigators' discretion, could be expected to interfere with the subject's health or with the trial parameters and/or put the subject at any unnecessary risk;

8) manifest signs or symptoms of clinically active allergic conjunctivitis [redacted]
9) have a history of glaucoma, ocular hypertension or an intraocular pressure (IOP) [redacted]
10) have used an investigational drug or medical device [redacted]
11) be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the trial duration, or has a positive urine pregnancy test at Visit 1.

Test Product, Dose and Mode of Administration, Batch Number:

- Reproxalap Ophthalmic Solution (0.25%)
- Reproxalap Ophthalmic Solution (0.5%)

Reference Therapy, Dose and Mode of Administration, Batch Number:

- Vehicle Ophthalmic Solution

Criteria for Evaluation:

Primary:

- Ocular itching score [redacted]

Key Secondary Endpoint:

- [redacted]

Additional Secondary Endpoints:

- Time to respons [redacted]
- Ocular itching score [redacted]

Safety Measures:

- Adverse Events (reported, elicited and observed)
- Visual Acuity at Distance Utilizing an ETDRS chart

Sponsor: Aldeyra Therapeutics, Inc.

Name of Finished Product: Reproxalap Ophthalmic Solutions (0.25% and 0.5%)

Name of Active Ingredient: reproxalap

Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

- Slit-lamp Biomicroscopy
- Intraocular Pressure
- Dilated Fundoscopy
- Conjunctival Redness

General Statistical Methods and Types of Analyses

Based on results of a Phase 2b clinical trial of ADX 102 in a CAC model [redacted], approximately [redacted] per randomized arm will be evaluated in ADX-102-AC-008. In the Phase 2b trial, [redacted]

Prior to database lock, the Sponsor will finalize a statistical analysis plan (SAP) that will detail all planned analyses. Any analyses conducted in addition to those specified in the SAP will be clearly documented as *post hoc*. A summary of the currently planned analyses for the primary and secondary outcome variables is found below.

[redacted]

[redacted]

Sponsor: Aldeyra Therapeutics, Inc.

Name of Finished Product: Reproxalap Ophthalmic Solutions (0.25% and 0.5%)

Name of Active Ingredient: reproxalap

Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

[redacted]

Tables and figures that convey the results of [redacted] will be provided.

[redacted]

The primary safety variable [redacted] All evaluations of safety will be described in the SAP.

Summary of Known and Potential Risks and Benefits to Human Subjects

Refer to Investigator's Brochure.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AC	allergic conjunctivitis
AE	adverse event
AUC	area under the curve
CAC	Conjunctival Allergen Challenge
CFR	Code of Federal Regulations
CRF	case report form
CRO	contract research organization
DHHS	Department of Health and Human Services
EKG	electrocardiogram
ERC	ethical review committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	generalized estimating equation
HIPAA	Health Information Portability and Accountability Act
IB	Investigators' brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IgE	immunoglobulin-E
IND	investigational new drug application
IOP	intraocular pressure
IP	investigational product
IRB	institutional/independent review board
ITT	intent to treat
LASIK	laser in situ keratomileusis
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
NCS	not clinically significant

NDA	new drug application
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
Ora-CAC®	Ora- Conjunctival Allergen Challenge
OS	left eye
OU	both eyes
OTC	over the counter
PHI	protected health information
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
VA	visual acuity

1 INTRODUCTION

Acute allergic conjunctivitis (AC), experienced by approximately 40% of the general population (Singh et al., 2010), is associated with Type I (immediate) hypersensitivity reactions. Type I reactions involve immunoglobulin E (IgE)-mediated release of histamine and other mediators from mast cells and basophils. Mast cell degranulation leads to release of inflammatory mediators and activation of enzymatic cascades generating pro-inflammatory mediators (Mishra et al, 2011). In the eye, release of a variety of mediators leads to inflammation of the conjunctival mucosa that also affects the cornea and eyelids, resulting in symptoms that include itching and burning, tearing, chemosis (conjunctival edema), conjunctival injection, hyperemia, eyelid edema, and mucus discharge. Although allergic conjunctivitis patients may also experience photophobia, allergic shiners (dark circles), and concurrent signs and symptoms of asthma or rhinitis, the absence of itching precludes a diagnosis of AC (Albrecht 2011).

Aldehydes are pro-inflammatory mediators of both allergic (TH2) and autoimmune (TH1) diseases, and elevated levels of toxic aldehydes are associated with allergic conjunctivitis and other ocular and systemic diseases (Bacsi et al 2005). Thus, aldehyde sequestering agents represent a novel and potentially broadly applicable therapeutic approach for the treatment of inflammation.

Reproxalap (the generic name for ADX-102) is a small molecule aldehyde trap in clinical development for ocular inflammatory disease. [redacted]

The symptoms of allergic conjunctivitis that occur within minutes of allergen exposure are likely due primarily to the release of histamine (Leonardi 2013), which peaks in tears around 5 minutes and significantly diminishes over 20 to 30 minutes (Ackerman et al. 2016). Immediately following, and to some degree concurrently with, the rapid rise and fall of histamine levels, the symptoms of allergic conjunctivitis are perpetuated by non-histaminic inflammatory mediators, including cellular infiltrate, cytokines, leukotrienes, proteases, and other factors (Leonardi 2013) likely to be diminished by aldehyde sequestering agents such as reproxalap, but not antihistamines.

[redacted]

Minutes Post–Challenge

Distinct from the acute histaminic phase of allergic conjunctivitis that is partially prophylactically modulated by antihistamines, the immediate post-histaminic inflammatory phase, which occurs [redacted] following allergen challenge, is a condition not studied with, and likely not well addressed by, available therapy. [redacted]

[redacted] Both concentrations of reproxalap were safe and well tolerated.

[redacted]

Based on the positive results of the Phase 2 clinical trials, Aldeyra plans to continue clinical development [redacted] Safety of the clinical dosing regimen in this trial is supported by a large number of pre-clinical and clinical, ocular and systemic, and toxicology and pharmacokinetic studies in which no serious safety concerns were noted.

2 STUDY OBJECTIVES

To evaluate the safety and efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) compared to Vehicle Ophthalmic Solution for the treatment of ocular itching associated with acute allergic conjunctivitis

3 CLINICAL HYPOTHESES

Based on the results of two vehicle-controlled, double-masked Phase 2 clinical trials, the Sponsor hypothesized that both concentrations of Reproxalap Ophthalmic Solution (0.25% and 0.5%) will be as safe as the Vehicle Ophthalmic Solution, and that at least one concentration of Reproxalap Ophthalmic Solution will be more effective than the Vehicle Ophthalmic Solution in the treatment of ocular itching associated with acute allergic conjunctivitis.

4 OVERALL STUDY DESIGN

The clinical trial is a multi-center, double-masked, randomized, parallel-group, vehicle-controlled Phase 3 clinical trial to evaluate the safety and efficacy of Reproxalap Ophthalmic Solution (0.25% and 0.5%) compared to Vehicle Ophthalmic Solution for the treatment of ocular itching associated with acute allergic conjunctivitis.

The trial will be comprised of [redacted] At the Screening Visit, subjects will sign the informed consent form, and an allergic skin test will be [redacted] be used to select a subject population [redacted] Subjects who meet the entry criteria for itching and redness response to CAC [redacted] will be randomized (1:1:1) [redacted] (Day 1, Enrollment/Randomization) to receive bilateral administration of either Reproxalap Ophthalmic Solution (0.25%), Reproxalap Ophthalmic Solution (0.5%), or Vehicle Ophthalmic Solution. [redacted] Subsequently, final exit procedures will be conducted and subjects will exit the trial.

5 STUDY POPULATION

5.1 NUMBER OF SUBJECTS (APPROXIMATE)

Approximately [redacted] will be screened in order to enroll [redacted] subjects at up to 8 sites.

5.2 STUDY POPULATION CHARACTERISTICS

Subjects at least 18 years of age of either gender and any race, who meet all of the inclusion criteria and none of the exclusion criteria

5.3 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 HIPAA form;
3) be willing and able to follow all instructions and attend all trial visits;
4) have a positive history of ocular allergies and a positive skin test reaction to a seasonal allergen [redacted] as confirmed by an allergic skin test [redacted]
5) be able and willing to avoid all disallowed medications [redacted]
6) be able and willing to discontinue wearing contact lenses [redacted]

7) have a calculated visual acuity [redacted];
8) agree to have urine pregnancy testing (for women considered capable of becoming pregnant, including all females who have experienced menarche and have not experienced menopause [as defined by amenorrhea for greater than 12 consecutive months] or have not undergone successful surgical sterilization [hysterectomy, bilateral tubal ligation, or bilateral oophorectomy]) performed at screening and exit visit; not be lactating; and agree to use a medically acceptable form of birth control throughout the trial duration;
9) have a positive bilateral CAC reaction [redacted]
10) have a positive bilateral CAC reaction [redacted]

5.4 EXCLUSION CRITERIA

Each subject <u>may not</u>:

1) have known contraindications or sensitivities to the use of the investigational product or any of its components;
2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters [redacted]
3) have had ocular surgical intervention [redacted]
4) have a known history [redacted]
5) have the presence of an active ocular infection [redacted]
6) use any of the following disallowed medications during the period indicated [redacted]

[redacted]

[1] not necessarily at the same time point

- [redacted]

7) have any significant illness [redacted] that, at the investigators' discretion, could be expected to interfere with the subject's health or with the trial parameters and/or put the subject at any unnecessary risk;
8) manifest signs or symptoms of clinically active allergic conjunctivitis [redacted]
9) have a history [redacted]
10) have used an investigational drug or medical device [redacted]
11) be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the trial duration, or has a positive urine pregnancy test at Visit 1.

5.5 WITHDRAWAL CRITERIA (IF APPLICABLE)

Subjects may voluntarily withdraw from the trial at any time. Subjects may also be withdrawn from the trial if any inclusion criteria are no longer met or if exclusion criteria are met post-randomization.

Any female will be removed from the trial should she become pregnant during the course of the trial, and she will undergo a pregnancy test at her exit visit for confirmation. The pregnancy test must be confirmed by two additional tests and confirmed by the principal investigator (or sub-investigator if the principal investigator is not present). If the test result is positive a second and third time, the principal investigator (or sub-investigator if the principal investigator is not present) will inform the subject. The investigator will document the outcome of the pregnancy and provide a copy of the documentation to the Sponsor.

Additionally, subjects may be discontinued for safety or sound medical reasons, as determined by the investigator/Sponsor (see Section 8.6).

Reason for withdrawal will be included in the electronic case report form (eCRF), and all efforts should be made to schedule the subject for an Exit Visit to complete exit procedures. Any subject withdrawn for the trial because of an AE will be followed until AE is resolved or as clinically required, and the investigator will prepare a written summary of the event and document the available follow-up information on the eCRF.

6 STUDY MEASURES

6.1 EFFICACY MEASURES

6.1.1 Primary Efficacy Endpoint(s)

- Ocular itching score [redacted]

6.1.2 Key Secondary Efficacy Endpoint

- Proportions of within-subject [redacted]

6.1.3 Additional Secondary Efficacy Endpoint(s)

- Time to response [redacted]
- Ocular itching score [redacted]

6.2 SAFETY MEASURES

- Adverse Events (reported, elicited and observed)
- Visual Acuity at Distance Utilizing an ETDRS chart
- Slit-lamp Biomicroscopy

- Intraocular Pressure
- Dilated Fundoscopy
- Conjunctival Redness

7 STUDY MATERIALS

7.1 STUDY TREATMENT(S)

7.1.1 Study Treatment(s)/ Formulation(s)

- Reproxalap Ophthalmic Solution (0.25%) (N=~100)
- Reproxalap Ophthalmic Solution (0.5%) (N=~100)
- Vehicle Ophthalmic Solution (N=~100)

7.1.2 Instructions for Use and Administration

- Subjects will be randomly assigned [redacted] to one of the three treatment groups to receive assigned investigational product bilaterally.

- Reproxalap Ophthalmic Solution (0.25% and 0.5%) and Vehicle Ophthalmic Solution will be supplied as sealed patient kits, with each kit containing two foil pouches and each foil pouch containing five single dose units, stored at 2°C to 8°C (36° F to 46°F) in an upright position. All test article(s) must be stored with access limited to the investigator and designated personnel.

- At the treatment visit, a new unopened pouch of topical ophthalmic solution will be used. The investigational drug product should be allowed to acclimate to room temperature [redacted] prior to administration.

- A trained trial technician will instill one drop of the assigned investigational product in each eye once [redacted]

- All investigational product must be secured in a locked container. Access will be limited to the investigator and designated personnel.

7.2 OTHER STUDY SUPPLIES

[redacted] will be used for pregnancy tests. Ora, Inc. will supply pregnancy kits.

The allergens used for skin testing and the conjunctival allergen challenge [redacted] will be [redacted]

The ocular anesthetic agent [redacted] and dilating drops used for the IOP and dilated fundoscopy respectively will be supplied by Ora, Inc.

Relief drops will be supplied by Ora, Inc.

Anti-itch cream and Calamine lotion for skin testing will also be supplied by Ora, Inc.

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 this trial.

8.1.2 Informed Consent

Prior to a subject's participation in the trial [redacted] the trial will be discussed with each subject, and subjects wishing to participate must sign an informed consent form (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board (IRB). Failure to obtain a signed ICF renders the subject ineligible for the trial. Subjects must be willing to return to the clinic [redacted].

Prior to the completion of the screening visit, if it is determined a subject did not meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process. Subjects may be re-screened a maximum of two times.

8.1.3 Washout Intervals

Prior to performing other trial procedures at Visit 1, trial staff will confirm that the subject has not used any of the following restricted products:

[redacted]

[redacted]

8.1.4 Procedures for Final Study Entry

Subjects must continue to meet all of the inclusion criteria and none of the exclusion criteria [redacted] to be enrolled in this trial.

8.1.5 Methods for Assignment to Treatment Groups:

All subjects screened for the trial who sign an ICF will be assigned a 3-digit screening number that will be entered in the Screening and Enrollment Log. Screening numbers will be assigned in a sequential order beginning with 001. Randomization will be used to avoid bias in the assignment of subjects to treatment and time point, to increase the likelihood that known and unknown subject attributes [redacted] are evenly balanced across treatment groups and across time points, and to enhance the validity of statistical comparisons.

Once a subject meets all qualification criteria [redacted] they will be enrolled and randomly assigned to masked treatment using a [redacted] Subjects will be assigned the lowest 4-digit randomization number available at the Investigative site within the appropriate stratum. The randomization number will be stratified [redacted] No randomization numbers will be skipped or omitted.

8.2 CONCURRENT THERAPIES

The use of any concurrent medication, prescription or over-the-counter, taken [redacted] 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 trial is not permitted.

8.2.1 Prohibited Medications/Treatments

- [redacted]
- [redacted]

[redacted]

8.2.2 Escape Medications

Subjects may receive either [redacted] after the skin test has been completed at the Screening Visit.

Cold compress should first be used in the management of allergic symptoms. Subjects may be prescribed [redacted] at the Investigator's discretion. [redacted]

Currently marketed [redacted] be administered to subjects by trained personnel [redacted] after all evaluations are completed.

8.2.3 Special Diet or Activities

Not Applicable.

8.3 EXAMINATION PROCEDURES

The following procedures will be conducted as listed in Section 8.3.1.

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

8.3.1.1 SCREENING VISIT (Day -61 to Day -22): Screening/ Informed Consent/ Skin Test

- *Informed Consent/HIPAA:* Prior to any changes in a subject's medical treatment and/or trial visit procedures, the trial will be discussed with each subject and subjects wishing to participate must give written informed consent and sign a HIPAA form.

  Prior to the completion of the screening visit, if it is determined a subject did not in fact meet certain washout criteria, the subject may be re-screened a later date. Subjects may be re-screened a maximum of two times.

- *Allergic Skin Test (if applicable):* A diagnostic test for allergic disease [redacted] will be performed according to Ora SOPs [redacted]

- *Demographic data and medical/medication/ocular and non-ocular history:* All demographic data, medical history, any medications, and any underlying condition(s) will be recorded. [redacted]

- *Review of Inclusion/Exclusion Criteria:* Washout time periods, if appropriate, will be confirmed (refer to Section 8.1.3)

- *Adverse Event Query*

- *Schedule Visit 1:* Qualifying subjects will be scheduled for Visit 1.

8.3.1.2 VISIT 1 (Day -21±3): Titration CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Urine Pregnancy Test (females of childbearing potential):* In order to be enrolled, women of childbearing potential must have a negative urine pregnancy test to continue in the trial, and must agree to use an adequate method of contraception for the duration of the trial.

- *Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score [redacted] in order to qualify.

- *Initial Ocular Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess initial ocular allergic signs and symptoms using the Ora-CAC® scales (see **Appendix 2**). [redacted]
- *Slit-lamp Biomicroscopy:* A slit-lamp examination will be performed in both eyes to exclude subjects with disallowed ocular conditions. Findings of abnormality that are not exclusionary should be recorded as Medical History.
- *Review of Inclusion/Exclusion Criteria:* A review of protocol inclusion and exclusion criteria will be confirmed for each subject.
- *Titration Conjunctival Allergen Challenge (CAC):* A conjunctival allergen challenge (CAC) will be performe [redacted]
  - [redacted]
  - [redacted]
- *Post-CAC Ocular Allergic Signs and Symptoms Assessment:* Upon completion of the initial titration CAC, subjects will receive [redacted]
- *IOP Measurement:* For subjects eliciting a positive post-CAC [redacted]
- *Dilated Fundoscopy:* For subjects eliciting a positive post-CAC reaction, [redacted]
- *Relief Drop Instillation:* To relieve any immediate discomfort caused by the allergic reaction, subjects may receive a dose of a currently marketed, [redacted] by trained trial personnel at the end of the visit.

- *Adverse Event Query*

- *Scheduling of Next Visit (Visit 2):* Subjects will be scheduled to return to the office in one week for Visit 2.

8.3.1.3 VISIT 2 (Day -14±3): Confirmation CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Visual Acuity Utilizing an ETDRS Chart*: The investigator should be notified if there is a clinically significant visual acuity decrease [redacted] Visual Acuity may be repeated in instances of significant decreases.

- *Pre-CAC Ocular Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess pre-CAC ocular allergic signs and symptoms using the Ora-CAC® scales. [redacted]

- *Slit-lamp Biomicroscopy*
- *Review of Inclusion/Exclusion Criteria*
- *Confirmation CAC*: For each qualified subject, one drop [redacted]
- *Post-CAC Ocular Allergic Signs and Symptoms Assessment:* Assessment of ocular itching will be made [redacted]
- *Relief Drop Instillation:* To relieve any immediate discomfort caused by the allergic reaction, [redacted] by trained trial personnel at the end of the visit.

- *Adverse Event Query*

- *Scheduling of Next Visit (Visit 3):* Subjects will be asked to return to the office [redacted]

8.3.1.4 VISIT 3 (Day 1): Enrollment/Randomization/10-Minutes pre-challenge dosing prior to CAC:

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Urine Pregnancy Test (for females of childbearing potential)*
- *Visual Acuity Utilizing an ETDRS Chart*: The investigator should be notified if there is a clinically significant visual acuity decrease [redacted]
- *Baseline Ocular Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess pre-CAC ocular allergic signs and symptoms using the Ora-CAC® scales (see **Appendix 2**). [redacted]
- *Slit-lamp Biomicroscopy*
- *Review Inclusion and Exclusion Criteria*
- *Randomization:* Subjects who meet all of the inclusion criteria and none of the exclusion criteria, and who otherwise qualify to continue in the trial, will be randomly assigned to [redacted]
- *Investigational Product Instillation:* A trained trial technician will instill the assigned investigational product according to the directions for use [redacted]
- *Conjunctival Allergen Challenge*: Approximately [redacted]
- *Post-CAC Ocular Allergic Signs and Symptoms Assessment:* Assessment of itching will be made [redacted]
- *Visual Acuity Utilizing an ETDRS Chart:* The investigator should be notified if there is a clinically significant visual acuity decrease [redacted]

[redacted]

- *Exit Slit-lamp Biomicroscopy*
- *Intraocular Pressure Measurement:* IOP will be measured [redacted]
- *Dilated Fundoscopy*
- *Relief Drop Instillation:* To relieve any immediate discomfort caused by the allergic reaction, subjects may receive a dose of a currently marketed, [redacted] by trained trial personnel at the end of the visit.
- *Adverse Event Query*
- *Study Exit*

Adverse Events [redacted] will be promptly reviewed by the investigator for accuracy and completeness. All Adverse Events will be documented on the appropriate CRF.

If a female has a positive pregnancy test during the trial, the investigator will notify Ora and the Sponsor/designee 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 these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

8.4 SCHEDULE OF VISITS, MEASUREMENTS AND DOSING

8.4.1 Scheduled Visits

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

If a subject is discontinued at a scheduled trial visit, the remaining assessments should be captured on the Unscheduled Visit/Early Exit Visit pages of the source document and corresponding eCRF.

8.4.2 Unscheduled Visits

For Unscheduled Visits, the reason for the visit should be clearly documented on the appropriate eCRF, including findings from all evaluations that are completed.

These visits may be performed to ensure subject safety. All information gathered at unscheduled visits should be recorded on the Unscheduled Visit/Early Exit Visit pages of the source document and corresponding eCRF.

Evaluations that may be conducted at an Unscheduled Visit (as appropriate, depending on the reason for the visit), include:

- Update of Medical/Medication History
- Urine Pregnancy Test
- Visual Acuity at Distance [redacted]
- Slit-lamp Biomicroscopy
- Intraocular Pressure
- Dilated Fundoscopy
- Assessment of Adverse Events
- Assessment of Conjunctival Redness

8.5 COMPLIANCE WITH PROTOCOL

Site staff will review concomitant medication and record any dosing regimen changes from previous visits. Concomitant medication information will be recorded in the source document and on the eCRF, [redacted]

Subjects who are inappropriately enrolled or no longer fulfill the trial eligibility criteria will be discontinued from the trial. The reason for discontinuation will be recorded as [redacted] in the source document and in the eCRF.

All protocol violations, [redacted] will be recorded in the subject's source document as well as the eCRF. Major protocol violations will be recorded in the subject's source document, entered in the eCRF for randomized subjects, and reported to the IRB, as per the applicable regulations.

8.6 SUBJECT DISPOSITION

8.6.1 Completed Subjects

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

8.6.2 Discontinued Subjects

Subjects may be discontinued prior to the completion of the trial for reasons including, but not limited to, the following:

- subject request/withdrawal,
- AEs,
- protocol violations,
- administrative reasons [redacted]
- Sponsor termination of trial, or
- any sound medical reason, as determined by the investigator.

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 CRF. Subjects who are discontinued from the trial will not be replaced.

8.7 STUDY TERMINATION

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

8.8 STUDY DURATION

This trial consists [redacted] over a period of [redacted]

8.9 MONITORING AND QUALITY ASSURANCE

During the course of the trial, an Ora monitor, or designee, will make routine site visits to review protocol compliance, assess trial drug accountability, and ensure the trial 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 trial monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, Ora quality assurance and/or its designees, as well as the Sponsor, 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 with special attention to data protection and subject confidentiality, to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

An Adverse Event (AE) is defined as any untoward medical occurrence associated with the use of an investigational product (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 or in response to an open question from trial 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.

Ocular complaints should not be addressed as AEs unless the complaint is outside the normal limits for allergic conjunctivitis symptoms after allergen exposure or is associated with clinical sequelae (i.e., adverse slit lamp examination finding).

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

9.1.1 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:

- [redacted]

[redacted]

[redacted]

9.1.2 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 characterizations will be used:

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

9.1.3 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.

AEs 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 and the Sponsor's Medical Monitor's determination.

9.2 SERIOUS ADVERSE EVENTS

An AE is considered serious if, in the view of either the investigator or Sponsor/designee, the AE 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/designee, the subject at immediate risk of death as a result of the AE. "Life threatening" 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; or admission to 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; and

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, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 PROCEDURES FOR REPORTING ADVERSE EVENTS

All AEs and their outcomes must be reported to Ora, the trial Sponsor/designee, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

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

9.3.2 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 CRF. The investigator is obligated to pursue and obtain information requested by Ora and/or the Sponsor/designee 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 the appropriate contact in the Study Manual 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 Ora and the Sponsor/designee 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 in a manner according to the IRB guidelines for reporting SAEs.

Collection of AEs/SAEs will begin at the time of informed consent and may be recorded up until 30 days post-instillation of IP.

9.4 PROCEDURES FOR UNMASKING (IF APPLICABLE)

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. The investigator should make every effort to contact Ora to

discuss the subject's emergency situation and the need to unmask a trial subject prior to unmasking IP.

If the investigator determines that emergency unmasking is necessary, the investigator should identify the given subject's trial drug kit, which contains a scratch-off laminate under which the treatment is identified along with the associated lot number. In order to unmask, the investigator should scratch off the laminate, using a flat object and applying pressure, to reveal the treatment assigned for that subject. The emergency unmasking should be performed by the designated site personnel. The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol. The investigator has the responsibility to contact Ora within 24 hours of breaking the blind.

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

9.5 TYPE AND DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

AEs will be followed until:

- resolution (return to baseline status or to 'normal'),
- stabilization of the event has occurred (no improvement or worsening expected by the Investigator), or
    - Note: The principal investigator determines whether the condition is to be chronic. Alternatively, the event may be determined to be resolved or resolved with sequelae.
- the event is otherwise explained, regardless of whether the subject is still participating in the trial.

The investigator will follow unresolved adverse events to resolution until the subject is lost to follow-up or until the adverse event is otherwise explained. If the subject is lost to follow-up, the investigator should make three reasonable attempts to contact the subject via telephone or certified mail. All follow-up will be documented in the subject's source document. Non-serious adverse events identified on the last scheduled contact must be recorded on the AE eCRF. The status of the AE must be noted and followed as aforementioned.

If the investigator becomes aware of any new information regarding a SAE (e.g., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to Ora Inc. within 24 hours. 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.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 STUDY POPULATIONS

10.1.1 Intent-to-Treat Population

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

10.1.2 Per-Protocol Population

The Per-Protocol (PP) population is [redacted]

10.1.3 Safety Population

The safety population includes [redacted]

10.2 GENERAL IMPUTATION METHODS

[redacted]

10.3 PRIMARY EFFICACY VARIABLES

- Ocular itching score [redacted]

10.4 KEY SECONDARY EFFICACY VARIABLES

- [redacted]

10.5 SECONDARY EFFICACY VARIABLES

- Time to response [redacted]

- Ocular itching score [redacted]

10.6 STATISTICAL HYPOTHESES

[redacted]

10.7 SAMPLE SIZE

Based on results of a Phase 2b clinical trial of ADX 102 in a CAC model [redacted]

10.8 DEMOGRAPHIC AND BASELINE MEDICAL HISTORY

The demographic and baseline medical history data will be summarized [redacted]

10.9 PRIMARY EFFICACY ANALYSES

The primary efficacy variable of ocular itch score [redacted]

10.10 SECONDARY EFFICACY ANALYSIS

The Key Secondary Endpoint [redacted]

Tables and figures that convey the results [redacted] Data listings will be prepared.

10.11 ADJUSTMENT FOR MULTIPLICITY

[redacted]

10.12 SAFETY ANALYSIS

The primary safety variable [redacted] All evaluations of safety will be described in the SAP.

10.13 STATISTICAL ANALYSES PLAN

Prior to database lock, the Sponsor will finalize a statistical analysis plan (SAP) that will detail all planned analyses. Any analyses conducted in addition to those specified in the SAP will be clearly documented as *post hoc*.

10.14 INTERIM ANALYSIS

No interim analyses are planned.

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

The trial will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in a manner that is generally consistent with the Declaration of Helsinki. In addition, conduct will adhere to all applicable local, state, and federal requirements relevant to the use of IP.

11.1 PROTECTION OF HUMAN SUBJECTS

11.1.1 Subject Informed Consent

Informed consent must take place before any trial specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject or from the subject's parent or legal guardian prior to enrollment into the trial.

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), the investigator must ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB, and that the informed consent is read, signed, and dated by all subjects currently or subsequently enrolled in the trial.

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.

11.1.2 Institutional Review Board (IRB) Approval

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

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

11.2 ETHICAL CONDUCT OF THE STUDY

The trial will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 SUBJECT CONFIDENTIALITY

All personal trial subject data collected and processed for the purposes of this trial 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 approving the trial, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the trial subject's original medical and trial 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 the trial 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.

11.4 DOCUMENTATION

Source documents may include [redacted] The investigator's copy of the eCRFs serves as the investigator's record of a subject's trial-related data.

11.4.1 Retention of Documentation

All trial-related correspondence, subject records, consent forms, records of the distribution and use of all IPs, 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 trial records, custody must be transferred to a person who will accept the aforementioned responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

11.5 LABELING, PACKAGING, STORAGE, ACCOUNTABILITY, AND RETURN OR DISPOSAL OF INVESTIGATIONAL PRODUCT

11.5.1 Labeling/Packaging

The subject kit will be labeled with the following:

- trial protocol number,
- contents,
- randomization number,
- subject number and initials (manually recorded),
- storage conditions,
- Investigational New Drug statement, and
- Sponsor's name, address and phone number.

The foil pouch label will be labeled with the following:

- trial protocol number,
- contents,
- randomization number,
- storage conditions,
- Investigational New Drug statement,
- manufacturer name and address, and
- Sponsor name, address, and phone number

11.5.2 Storage of Investigational Product

[redacted]

The IP must be stored in a secure area accessible only to the investigator and his/her designees. The IP will be administered only to subjects entered into the clinical trial, in accordance with the conditions specified herein.

11.5.3 Accountability of Investigational Product

The IP is to only be prescribed by the principal investigator or his/her named sub-investigator(s), and is only to be used in accordance with this protocol. To receive IP, the IP must be distributed only to subjects properly qualified under the conditions specified herein.

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 trial. A detailed inventory must be completed for the IP and available for Sponsor's review during the course of the trial.

11.5.4 Final accountability and Disposal of Investigational Product

At the conclusion of the trial, IP reconciliation will be performed and all remaining IP will be destructed and disposed of according to clinical site's SOP. Sponsor will be provided with a final accounting of IP for approval prior to destruction.

11.6 RECORDING OF DATA ON SOURCE DOCUMENTS AND CASE REPORTS FORMS (CRFS)

The investigator is responsible for ensuring trial data are completely and accurately recorded on each subject's eCRF, source document, and all trial-related material. All trial 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.

The Electronic Data Capture for this study will be iMedNet, with access settings configured that conform with 21 CFR Part 11 requirements. Only staff that has been trained will have access to the system. Subject data will be provided to the sites by CD/DVD at the end of the trial.

11.7 HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

11.8 PUBLICATIONS

Authorship and manuscript composition will reflect cooperation among all parties involved in the trial. Authorship will be established before writing the manuscript. Ora and the Sponsor will have the final decision regarding the manuscript and publication.

12 REFERENCES

Ackerman, S., Smith, L.M., and Gomes, P.J. (2016). Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. *Ther. Adv, Chronic Dis. 7*(1), 52-67.

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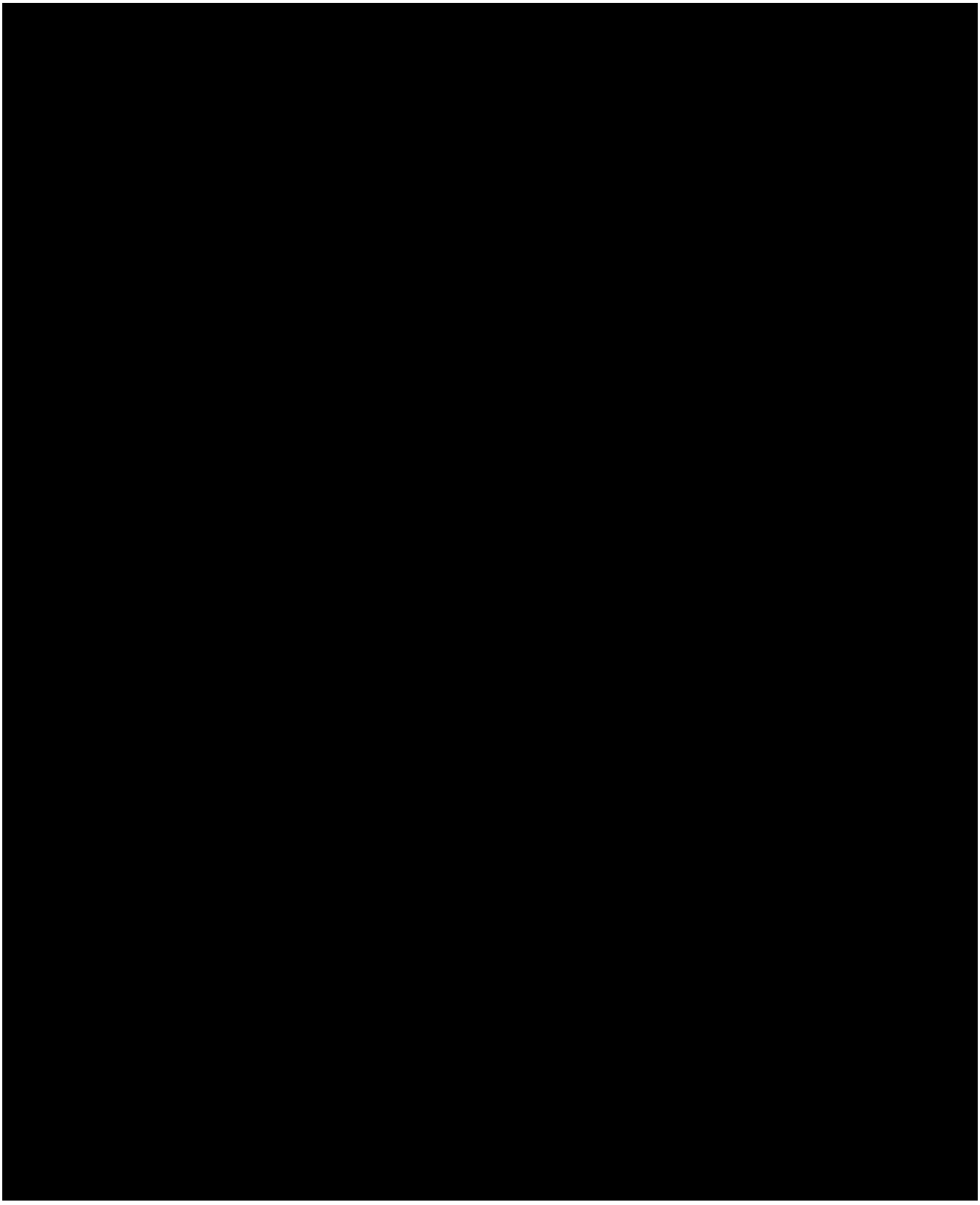
Leonardi, A. (2013). Allergy and allergic mediators in tears. *Exp. Eye Res. 117*, 106-117.

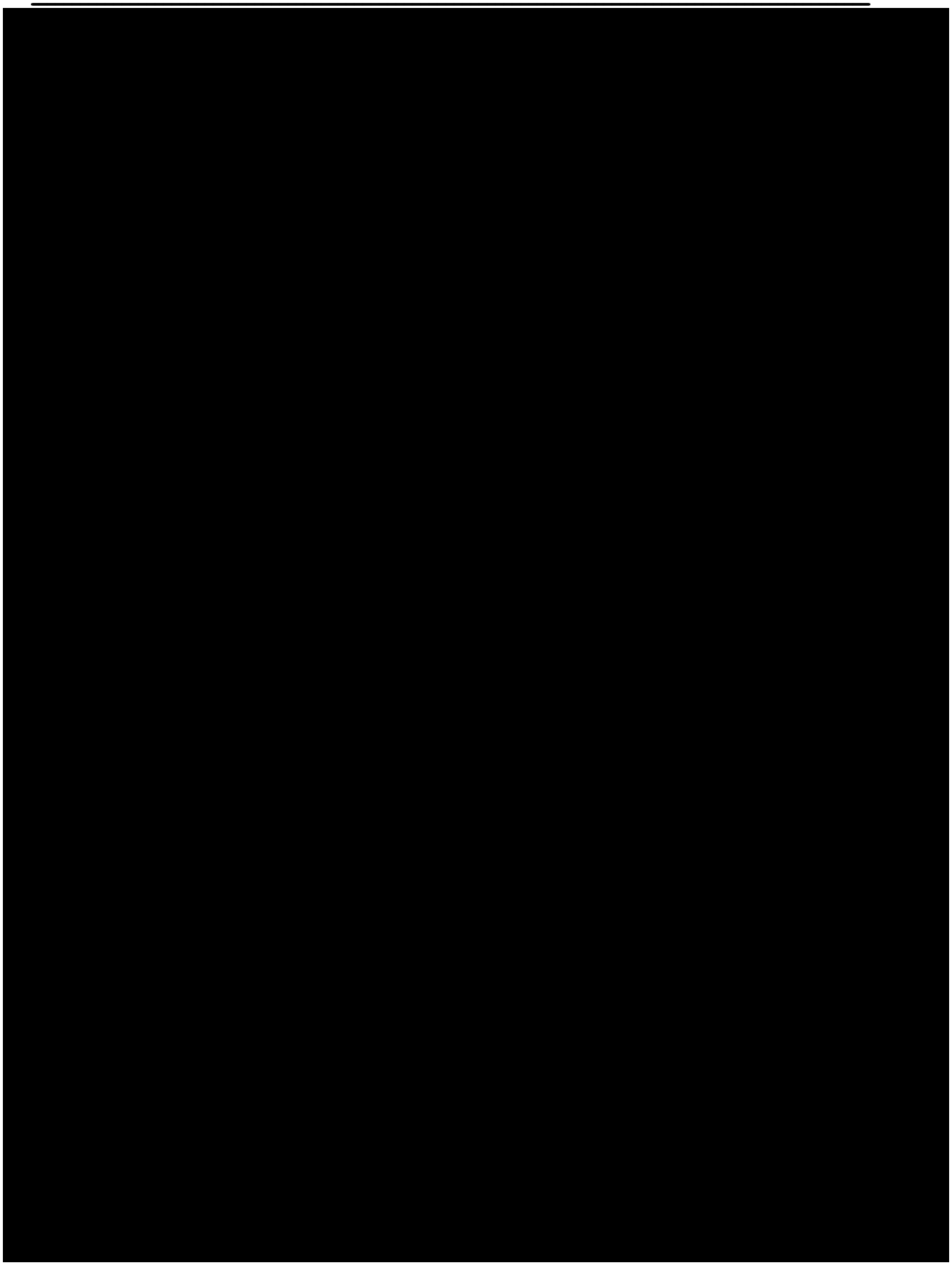
Mishra G, Tamboli V, Jwala J, Mitra A. Recent patents and emerging therapeutics in the treatment of allergic conjunctivitis. *Inflamm Allergy Drug Discov*. 2011;5(1):26-36.

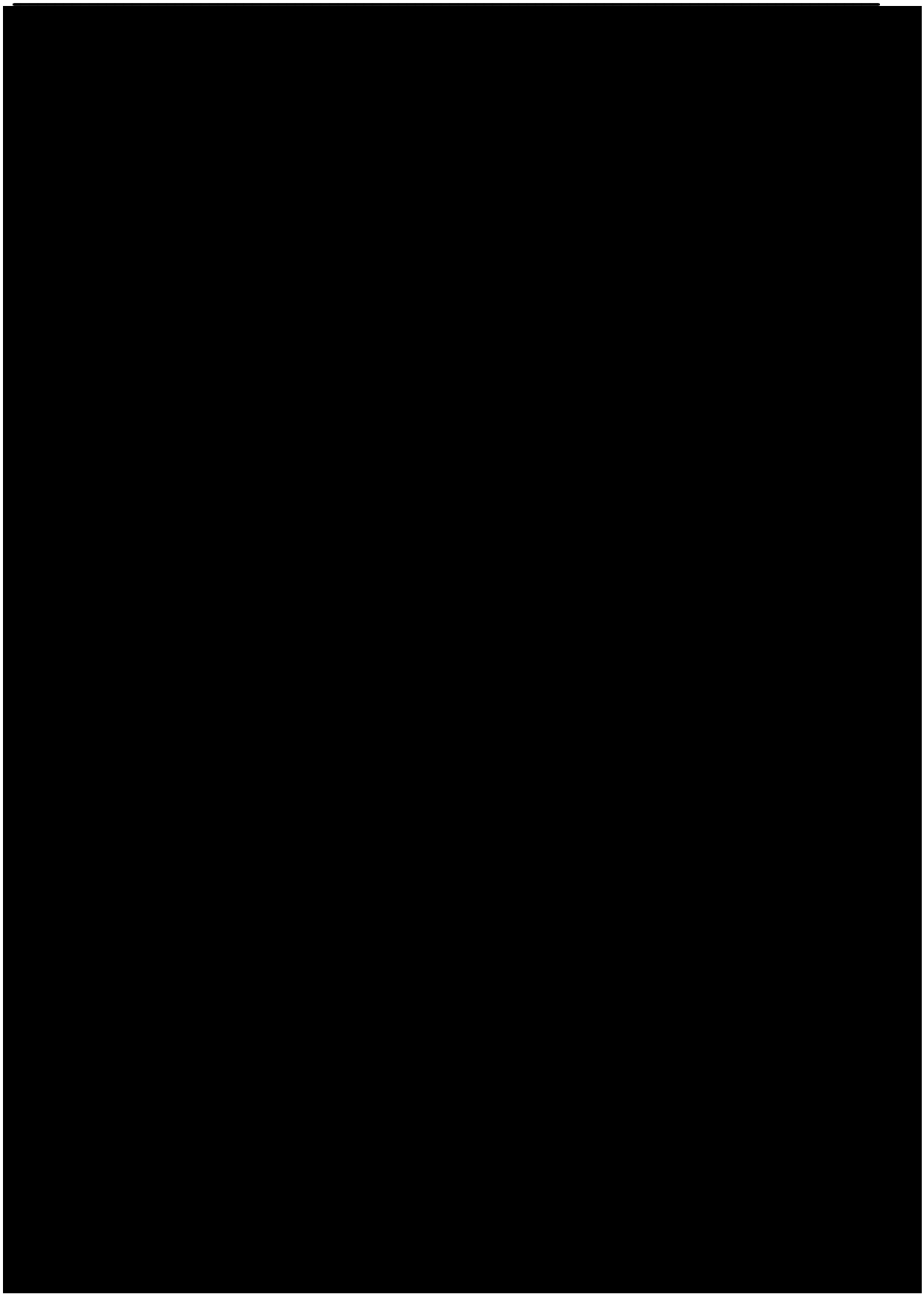
Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. *J Allergy Clin Immunol*. 2010;126(4):778-783.

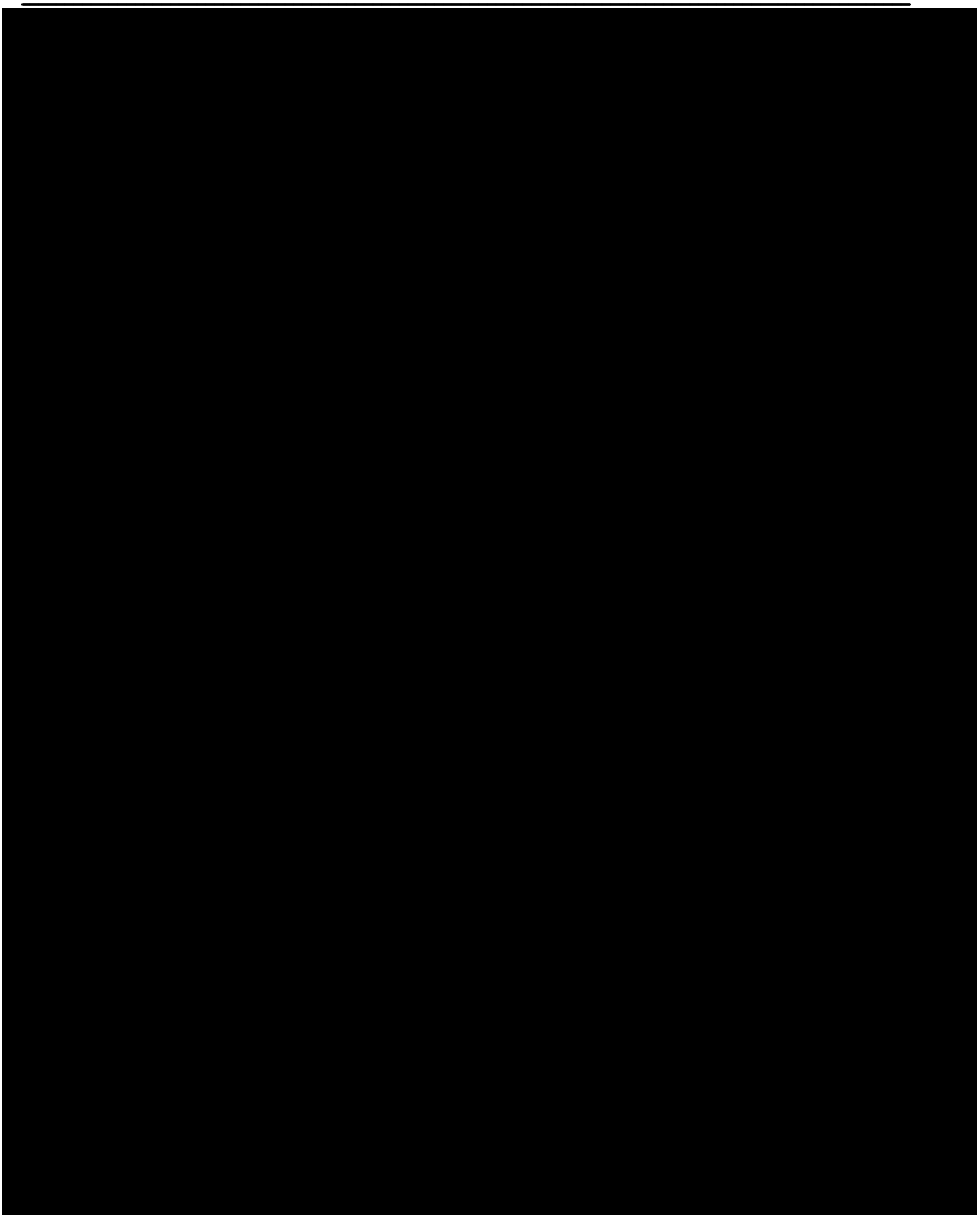
APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

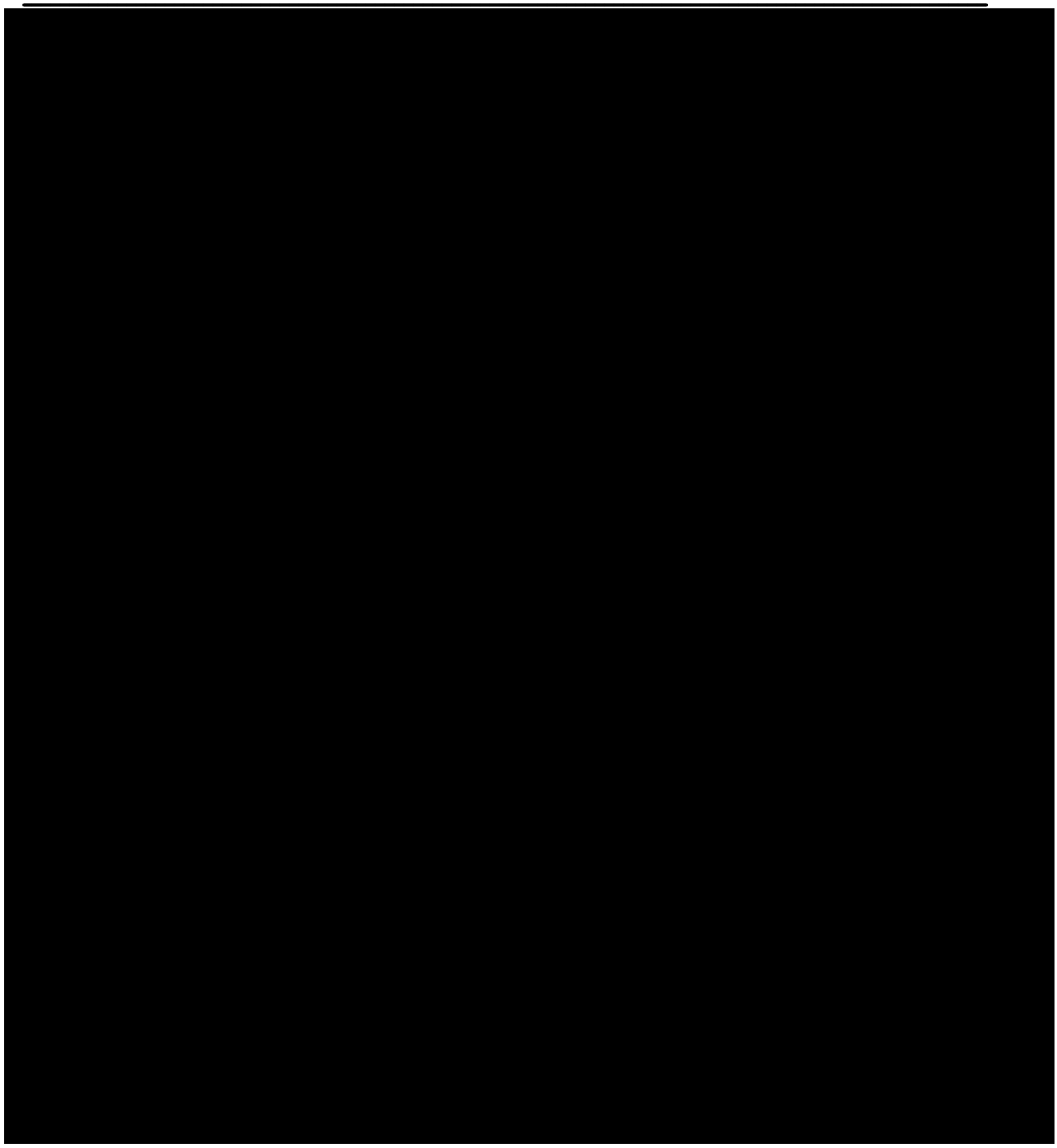
APPENDIX 2: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

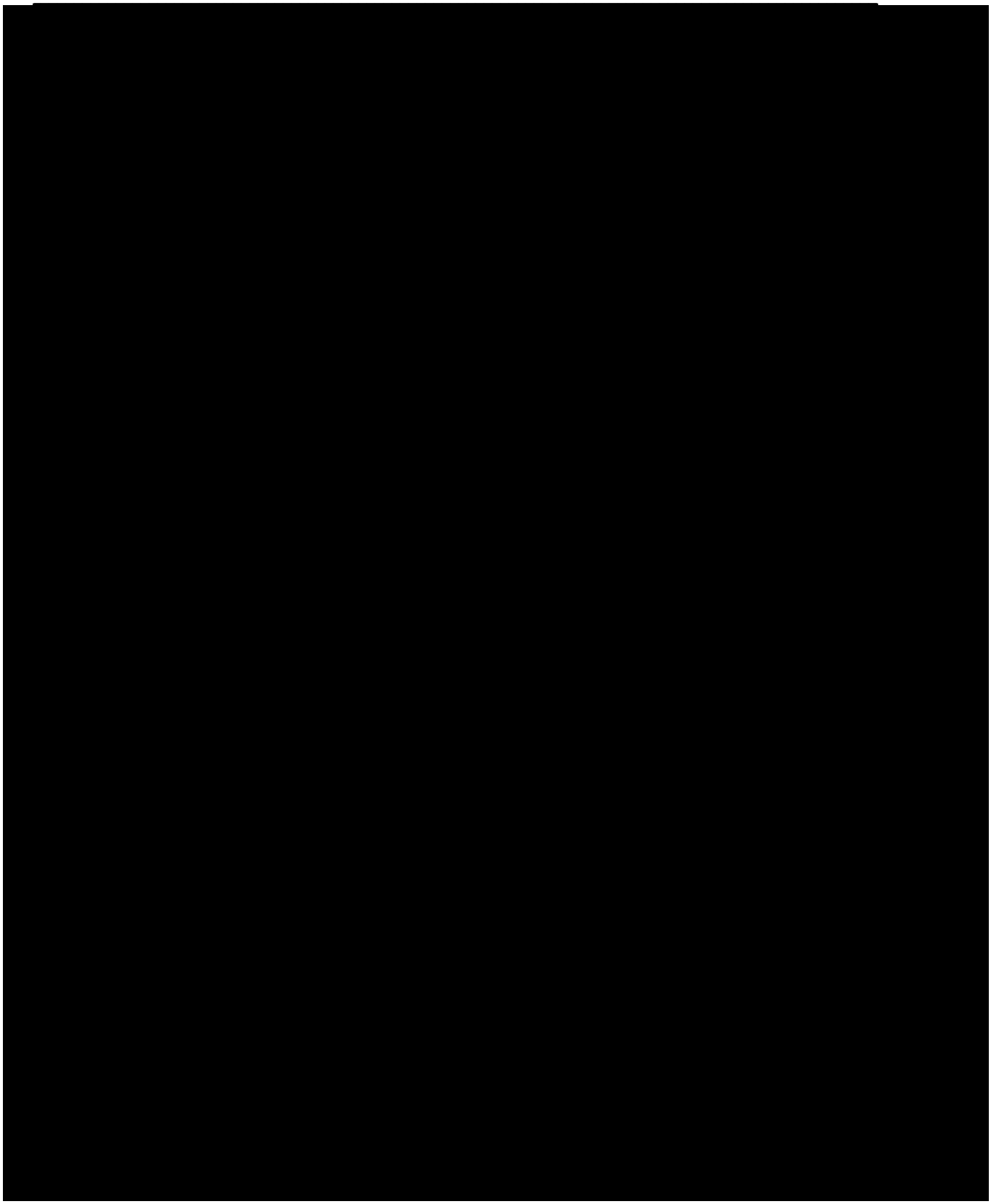












APPENDIX 3: INVESTIGATIONAL PRODUCT COMPOSITION/ DESIGN

Reproxalap Ophthalmic Solution for topical ophthalmic delivery is formulated as a sterile, preservative free, aqueous solution for topical ocular delivery. The drug product will be supplied in single-dose units packaged in blow fill seal (BFS) containers.

The trial drug consists [redacted]

[redacted]

APPENDIX 4: HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

APPENDIX 5: PROTOCOL AMENDMENT SUMMARY

Not Applicable.

APPENDIX 6: ORA APPROVALS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3, Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis
Protocol Number:	ADX-102-AC-008
Final Date:	15 February 2018

This clinical trial protocol was subject to critical review and has been approved by Ora, Inc. The following personnel contributed to writing and/or approving this protocol.

APPENDIX 7: SPONSOR (ALDEYRA) APPROVALS

Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3, Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

Protocol Number: ADX-102-AC-008

Final Date: 15 February 2018

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

[redacted]

APPENDIX 8: INVESTIGATOR'S SIGNATURE

Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3, Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

Protocol Number: ADX-102-AC-008

Final Date: 15 February 2018

I agree to implement and conduct the trial 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.