1 CLINICAL TRIAL PROTOCOL: ADX-102-AC-004

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2b Evaluation of the Onset and Duration of ADX-102 Ophthalmic Drops (0.5% and 0.1%) Compared to Vehicle of ADX-102 Ophthalmic Drops in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis
Protocol Number:	ADX-102-AC-004
Name of Test Drug /Investigational Product:	ADX-102 Ophthalmic Drops (0.5% and 0.1%)
[redacted]	[redacted]
Indication Studied:	Acute allergic conjunctivitis
Development Phase:	2b
Brief Description:	Multi-center, double-masked, randomized, vehicle-controlled, phase 2b CAC study.
Name of Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Ave. Lexington, MA 02421
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, Third Floor Andover, MA 01810
IRB/IEC:	[redacted]

	Date
Original Protocol:	19 October 2016

Statement of Compliance with Good Clinical Practice

This study will be performed in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP).

Confidentiality Statement

[redacted]

[redacted]	[redacted]

[redacted]

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

2 SYNOPSIS

Sponsor: Aldeyra Therapeutics, Inc.
Name of Finished Product: ADX-102
Name of Active Ingredient: ADX-102 Ophthalmic Drops (0.5%) and ADX-102 Ophthalmic Drops (0.1%)
Protocol Title: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2b Evaluation of the Onset and Duration of ADX-102 Ophthalmic Drops (0.5% and 0.1%) Compared to Vehicle of ADX-102 Ophthalmic Drops in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis
Protocol Number: ADX-102-AC-004
Investigator: Multi-Center
Study Phase of Development: 2b
Objectives: To evaluate the efficacy of ADX-102 ophthalmic drops (0.5% and 0.1%) compared to vehicle of ADX-102 ophthalmic drops for the treatment of the signs and symptoms of acute allergic conjunctivitis.
Methodology:
Structure: Multi-center, double-masked, randomized, vehicle-controlled, Phase 2b study to evaluate the efficacy of ADX-102 ophthalmic drops (0.5% and 0.1%) compared to vehicle of ADX-102 ophthalmic drops for the treatment of the signs and symptoms of acute allergic conjunctivitis.
Duration: This study consists of 4 office visits over a period of approximately 5 weeks. *Screening Period:* Screening will be approximately 3 weeks in duration. At Visit 1, subjects will undergo an allergen titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-CAC will undergo the confirmation CAC at Visit 2 using the same allergen they qualified with at Visit 1. *Treatment Period:* Treatment will begin at Visit 3 after subjects are randomized. At this visit, subjects will receive an in-office dose of the treatment that they were randomized to receive. Subjects will receive 1 additional dose at Visit 4.
Summary of Visit Schedule: • Visit 1 (Day -21 ± 3): Screening/Titration CAC • Visit 2 (Day -14 ± 3): Confirmation CAC • Visit 3 (Day 1): Enrollment/Randomization/ 1-Hour (+5 Minutes) Duration of Action CAC • Visit 4 (Day 15 ± 3): 10-Minutes Onset of Action CAC
Measures Taken to Reduce Bias: Randomization will be used to avoid bias in the assignment of subjects to investigational product, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. In addition, randomization will be stratified by average post-CAC itching scores [redacted] at baseline (Visit 2) to ensure balance for the primary endpoint of ocular

Sponsor: Aldeyra Therapeutics, Inc.
Name of Finished Product: ADX-102
Name of Active Ingredient: ADX-102 Ophthalmic Drops (0.5%) and ADX-102 Ophthalmic Drops (0.1%)
Protocol Title: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2b Evaluation of the Onset and Duration of ADX-102 Ophthalmic Drops (0.5% and 0.1%) Compared to Vehicle of ADX-102 Ophthalmic Drops in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis
itching. Finally, masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.
Study Population Characteristics
Number of Subjects: Approximately 375 subjects will be screened in order to enroll approximately 150 subjects at up to 5 sites.
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 study visits; 4) have a positive history of ocular allergies and a positive skin test reaction to a [redacted] allergen [redacted] as confirmed by an allergic skin test within the [redacted]; 5) be able and willing to avoid all disallowed medications for the appropriate washout period and during the study (see exclusion 6); 6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to and during the study trial period; 7) have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart; 8) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at screening (must be negative) and exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration and for at least 14 days prior to the instillation of investigational product (Visit 3). Women considered capable of becoming pregnant include 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); 9) have a positive bilateral CAC reaction [redacted] within 10

[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.

Sponsor: Aldeyra Therapeutics, Inc.

Name of Finished Product: ADX-102

Name of Active Ingredient: ADX-102 Ophthalmic Drops (0.5%) and ADX-102 Ophthalmic Drops (0.1%)

Protocol Title: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2b Evaluation of the Onset and Duration of ADX-102 Ophthalmic Drops (0.5% and 0.1%) Compared to Vehicle of ADX-102 Ophthalmic Drops in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

(±2) minutes of instillation of the last titration of allergen at Visit 1;

10) have a positive bilateral CAC reaction [redacted] for at least two out of the first three time points[1] following the challenge at Visit 2.

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 (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months;
4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit;
6) use any of the following disallowed medications during the period indicated **prior to Visit 1** and during the study:

<u>72 hours</u>
- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast cell stabilizers, H_1 antihistamine-vasoconstrictor drug combinations

<u>7 days</u>
- decongestants
- monoamine oxidase inhibitors
- all other topical ophthalmic preparations (including artificial tears)
- lid scrubs
- topical prostaglandins or prostaglandin derivatives
- ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs)

<u>14 days</u>
- inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers

<u>45 days</u>
- depo-corticosteroids

[1] not necessarily at the same time point

Sponsor: Aldeyra Therapeutics, Inc.

Name of Finished Product: ADX-102

Name of Active Ingredient: ADX-102 Ophthalmic Drops (0.5%) and ADX-102 Ophthalmic Drops (0.1%)

Protocol Title: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2b Evaluation of the Onset and Duration of ADX-102 Ophthalmic Drops (0.5% and 0.1%) Compared to Vehicle of ADX-102 Ophthalmic Drops in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

2 months

- immunotherapeutic agents: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage may change during the clinical trial.

Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered by trained study personnel to subjects at the end of Visits 1, 2, 3, and 4, after all evaluations are completed.

7) have any significant illness (e.g. any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels could be expected to interfere with the subject's health or with the study parameters and/or put the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
8) manifest signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 1, 2, or 3 [redacted]);
9) have a history of glaucoma, ocular hypertension or an intraocular pressure (IOP) that is greater than 24 mmHg at Visit 1;
10) have planned surgery (ocular or systemic) during the trial period or within 30 days after;
11) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial;
12) be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for 14 days prior to the installation of investigational product, or has a positive urine pregnancy test at Visit 1.

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

- ADX-102 Ophthalmic Drops (0.5%)
- ADX-102 Ophthalmic Drops (0.1%)

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

- Vehicle of ADX-102 Ophthalmic Drops

Criteria for Evaluation:

Efficacy Measures:

Primary:

- Ocular itching evaluated by the subject at 10(±1), 15(±1), and 20(±1) minutes post-CAC at Visits 3 and 4 (0-4 scale, allowing half unit increments)

Sponsor: Aldeyra Therapeutics, Inc.

Name of Finished Product: ADX-102

Name of Active Ingredient: ADX-102 Ophthalmic Drops (0.5%) and ADX-102 Ophthalmic Drops (0.1%)

Protocol Title: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2b Evaluation of the Onset and Duration of ADX-102 Ophthalmic Drops (0.5% and 0.1%) Compared to Vehicle of ADX-102 Ophthalmic Drops in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

[redacted]

Safety Measures:

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

General Statistical Methods and Types of Analyses

Approximately 150 subjects will be randomized at Visit 3, or approximately 50 subjects per treatment arm. [redacted]

[redacted]

Quantitative variables will be summarized using descriptive statistics, that is, number of observations, mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages. Statistical testing will be performed at a two-sided significance level of alpha = 0.05. For all analyses, comparisons will be made between each dose of ADX-102 Ophthalmic Drops and vehicle.

Sponsor: Aldeyra Therapeutics, Inc.
Name of Finished Product: ADX-102
Name of Active Ingredient: ADX-102 Ophthalmic Drops (0.5%) and ADX-102 Ophthalmic Drops (0.1%)
Protocol Title: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2b Evaluation of the Onset and Duration of ADX-102 Ophthalmic Drops (0.5% and 0.1%) Compared to Vehicle of ADX-102 Ophthalmic Drops in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis
The primary efficacy variable is measured at Visit 3 (1 hour post treatment) and Visit 4 (10 minutes post treatment). [redacted]
[redacted]
[redacted]
The primary safety variable is the incidence of subjects with any adverse event during the entire study. The percentage of subjects with specific treatment-emergent adverse events will be summarized for each treatment group. A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments. Incidence will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and preferred term within each system organ class. The secondary safety variables of visual acuity, slit lamp biomicroscopy, IOP, and dilated fundoscopy will be summarized descriptively.
Summary of Known and Potential Risks and Benefits to Human Subjects Refer to Investigator's Brochure.

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LIST OF ABBREVIATIONS

AC	allergic conjunctivitis
ADE	adverse device effect
AE	adverse event
ANCOVA	analysis of covariance
BOCF	baseline observation carried forward
CAC	conjunctival allergen challenge
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CRO	contract research organization
DHHS	Department of Health and Human Services
ECG	electrocardiogram
ERC	ethical review committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
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
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution

LS	least squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mmHg	millimeters of mercury
NCS	not clinically significant
NDA	new drug application
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
Ora-CAC®	conjunctival allergen challenge
OS	left eye
OU	both eyes
OTC	over the counter
PHI	protected health information
PP	per protocol
ROPI	Report of Prior Investigations
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
VA	visual acuity

3 INTRODUCTION

4 STUDY OBJECTIVES

To evaluate the efficacy of ADX-102 ophthalmic drops (0.5% and 0.1%) compared to vehicle of ADX-102 ophthalmic drops for the treatment of the signs and symptoms of acute allergic conjunctivitis.

5 CLINICAL HYPOTHESES

It is hypothesized that at least one concentration of ADX-102 ophthalmic drops will be more effective than vehicle of ADX-102 in the treatment of the signs and symptoms of acute allergic conjunctivitis.

6 OVERALL STUDY DESIGN

This is a multi-center, double-masked, randomized, vehicle-controlled, phase 2b study evaluating the efficacy of ADX-102 ophthalmic drops (0.5% and 0.1%) compared to vehicle of ADX-102 ophthalmic drops for the treatment of the signs and symptoms of acute allergic conjunctivitis.

The trial will comprise of 4 office visits over a period of approximately 5 weeks. Visits 1 and 2 will be used to select a subject population that responds reproducibly to two CACs administered approximately 7 days apart. Subjects who meet the entry criteria for itching and redness response to CAC at Visits 1 and 2 will be randomized (1:1:1) at Visit 3 (Day 1, Enrollment/Randomization) to receive either ADX-102 ophthalmic drops (0.5%), ADX-102 ophthalmic drops (0.1%), or vehicle of ADX-102 ophthalmic drops bilaterally. Subjects will undergo the 1-hour (+5 minutes) duration of action CAC from the time of their instillation. Subjects will return approximately 14 days later for Visit 4 (Day 15± 3, 10-Minutes Onset of Action CAC), at which time they will be treated with the same treatment they received at Visit 3 and challenged approximately 10 minutes after dosing. At Visit 4, final exit procedures will also be conducted and subjects will exit the study.

7 STUDY POPULATION

7.1 NUMBER OF SUBJECTS (APPROXIMATE)

Approximately 375 subjects will be screened in order to enroll approximately 150 subjects at up to 5 sites.

7.2 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.

7.3 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 study visits;
4) have a positive history of ocular allergies and a positive skin test reaction to a [redacted] allergen [redacted] as confirmed by an allergic skin test within the [redacted]
5) be able and willing to avoid all disallowed medications for the appropriate washout period and during the study (see exclusion 6);
6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to and during the study trial period;
7) have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart;
8) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at screening (must be negative) and exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[3] throughout the study duration and for at least 14 days prior to the instillation of investigational product (Visit 3). Women considered capable of becoming pregnant include 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);
9) have a positive bilateral CAC reaction [redacted] within 10 (±2) minutes of instillation of the last titration of allergen at Visit 1;
10) have a positive bilateral CAC reaction [redacted] at least two out of the first three time points[4] following the challenge at Visit 2.

[3] 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.
[4] not necessarily at the same time point

7.4 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 (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months;
4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit;
6) use any of the following disallowed medications during the period indicated **prior to Visit 1** and during the study:

   72 hours
   - systemic or ocular H_1 antihistamine, H_1 antihistamine/mast cell stabilizers, H_1 antihistamine- vasoconstrictor drug combinations

   7 days
   - decongestants
   - monoamine oxidase inhibitors
   - all other topical ophthalmic preparations (including artificial tears)
   - lid scrubs
   - topical prostaglandins or prostaglandin derivatives
   - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs)

   14 days
   - inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers

   45 days
   - depo-corticosteroids

   2 months
   - immunotherapeutic agents: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage may change during the clinical trial.

   Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered by trained study personnel to subjects at the end of Visits 1, 2, 3, and 4, after all evaluations are completed.
7) have any significant illness (e.g. any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels could be expected to interfere with the subject's health or with the study parameters and/or put

the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;

8) manifest signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 1, 2, or 3 [redacted]
9) have a history of glaucoma, ocular hypertension or an intraocular pressure (IOP) that is greater than 24 mmHg at Visit 1;
10) have planned surgery (ocular or systemic) during the trial period or within 30 days after;
11) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial;
12) be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for 14 days prior to the installation of investigational product, or has a positive urine pregnancy test at Visit 1.

7.5 WITHDRAWAL CRITERIA (IF APPLICABLE)

Subjects may voluntarily withdraw from the study at any time. Subjects who manifest signs or symptoms of clinically active allergic conjunctivitis [redacted] prior to the CAC, in either eye at the start of Visit 4, will be withdrawn from the study. Subjects may also be withdrawn from the study if any inclusion criteria are no longer met or if exclusion criteria are met post-randomization.

Any female will be removed from the study should she become pregnant during the course of the study, 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 follow-up and document the outcome of the pregnancy and provide a copy of the documentation to the Sponsor. The Ora Pregnancy Report Form will be used to report a pregnancy and follow-up.

Additionally, subjects may be discontinued for safety or sound medical reasons as determined by the investigator (see Section 10.6).

8 STUDY MEASURES

8.1 EFFICACY MEASURES

8.1.1 Primary Efficacy Measure(s)

- Ocular itching evaluated by the subject at 10(±1), 15(±1), 20(±1) minutes post-CAC at Visits 3 and 4 (0-4 scale, allowing half unit increments)

8.1.3 Criteria for Effectiveness

To demonstrate the clinical effectiveness for ocular itching, ADX-102 Ophthalmic Drops will need to show clinical superiority over vehicle by at least 0.5 units of a 5 point scale for the 10(±1), 15(±1) and 20(±1) minutes post-CAC time points within a visit, and at least 1 unit for the majority of the same three post-CAC time points within a visit for each treatment comparison.

8.2 SAFETY MEASURES

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

9 STUDY MATERIALS

9.1 STUDY TREATMENT(S)

9.1.1 Study Treatment(s)/ Formulation(s)

- ADX-102 Ophthalmic Drops (0.5%) (N=~50)
- ADX-102 Ophthalmic Drops (0.1%) (N=~50)
- Vehicle of ADX-102 Ophthalmic Drops (N=~50)

9.1.2 Instructions for Use and Administration

- Subjects will be randomly assigned (stratified randomization based on average post-CAC itching scores at Visit 2) at Visit 3 to one of the three treatment groups to receive assigned investigational product bilaterally.
- [redacted]
- At each treatment visit, a new unopened pouch of Ophthalmic Drops will be used. [redacted]
- [redacted]
- All investigational product must be secured in a locked container with access limited to the investigator and designated personnel.

9.2 OTHER STUDY SUPPLIES

Clarity HCG (RAC Medical Boca Raton, FL) will be used for pregnancy tests. Ora, Inc. will supply these pregnancy kits.

[redacted]

The ocular anesthetic agent (Fluress) 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.

10 STUDY METHODS AND PROCEDURES

10.1 SUBJECT ENTRY PROCEDURES

10.1.1 Overview

Subjects as defined by the criteria in section 7.2, 7.3, and 7.4 will be considered for entry into this study.

10.1.2 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 (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board. Failure to obtain a signed ICF renders the subject ineligible for the study.

Informed consent may be obtained within 30 days prior to Visit 1; however, informed consent must be obtained prior to Visit 1 if any of the following criteria are determined during the telephone screening process:

- Washout of certain medications is necessary
- Sufficient time of discontinuation of contact lens wear is necessary
- Post-operative period

Medical/medication history, demographics, skin test and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).

10.1.3 Washout Intervals

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

72 hours
- Contact lenses
- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast cell stabilizers, H_1 antihistamine- vasoconstrictor drug combinations

7 days
- decongestants
- monoamine oxidase inhibitors
- all other topical ophthalmic preparations (including artificial tears)
- lid scrubs
- topical prostaglandins or prostaglandin derivatives
- ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs)

14 days
- inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers

45 days

- depo-corticosteroids

2 months

- immunotherapeutic agents: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage may change during the clinical trial.

Note: Currently marketed over-the-counter anti-allergy eye drops (ie, anti-histamine/vasoconstrictor combination products such as Visine®-A®) may be administered by trained study personnel to subjects at the end of Visits 1, 2, 3, and 4, after all evaluations are completed.

10.1.4 Procedures for Final Study Entry

Subjects must continue to meet all of the inclusion criteria and none of the exclusion criteria prior to Visit 3 to be enrolled in the study.

10.1.5 Methods for Assignment to Treatment Groups:

All subjects screened for the study 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 (e.g., demographics and baseline characteristics) 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 at Visit 3 (Day 1), they will be enrolled and randomly assigned to masked treatment using a 1:1:1 (ADX-102 ophthalmic drops [0.5%]: ADX-102 ophthalmic drops [0.1%]: vehicle of ADX-102 ophthalmic drops) assignment ratio. 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 by the average post-CAC itching scores [redacted] at baseline (Visit 2) to ensure balance for the primary endpoint of ocular itching. No randomization numbers will be skipped or omitted.

10.2 CONCURRENT THERAPIES

[redacted]

10.2.1 Prohibited Medications/Treatments

[redacted]

10.2.2 Escape Medications

[redacted]

10.2.3 Special Diet or Activities

Not Applicable.

10.3 EXAMINATION PROCEDURES

The following procedures will be conducted as listed in Section 10.3.1.

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

10.3.1.1 VISIT 1 (Day -21±3): Screening /Titration CAC

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

Informed consent may be obtained within 30 days prior to Visit 1, however, informed consent must be obtained prior to Visit 1 if any of the following criteria are determined during the telephone screening process:

- Proper washout of certain medications is necessary
- Sufficient time of discontinuation of contact lens wear is necessary
- Post-operative period

Medical/medication history, demographics, skin test and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).

- *Allergic Skin Test:* A diagnostic test for allergic disease (skin test) will be performed for subjects without documentation of a positive test within the [redacted].
- *Demographic data and medical/medication/ocular and non-ocular history:* Collect and record all demographic data, medical history, any medications, and any underlying condition(s). Current underlying conditions, including those that began within the last forty five (45) days, which may have been resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within forty five (45) days prior to screening.
- *Urine Pregnancy Test (for females of childbearing potential):* Women of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception for the duration of the study in order to be enrolled and for at least 14 days prior to the instillation of investigational product (Visit 3).
- *Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score of 0.7 logMAR or better in each eye in order to qualify.
- *Initial Ocular Allergic Signs and Symptoms Assessment:* [redacted]
- *Slit Lamp Biomicroscopy:* A slit-lamp examination will be performed in both eyes to exclude subjects with disallowed ocular conditions. Findings of abnormality which 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):* [redacted]

- [redacted]
- [redacted]
- [redacted]
- *IOP Measurement:* Intraocular Pressure (IOP) will be measured in each eye by contact tonometry, for qualified subjects.
- *Dilated Fundoscopy:* A dilated fundoscopy will be performed by the Investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology, for qualified subjects.
- [redacted]
- *Scheduling of Next Visit (Visit 2):* Subjects will be scheduled to return to the office in 1 week for Visit 2.

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

- *Update of Medical/Medication History*
- *Visual Acuity Utilizing an ETDRS Chart:* The Investigator should be notified if there is a clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1.
- *Pre-CAC Ocular Allergic Signs and Symptoms Assessment:* [redacted]
- *Slit Lamp Biomicroscopy*
- *Review of Inclusion/Exclusion Criteria*

- *Confirmation CAC*: [redacted]
- *Post-CAC Ocular Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 10(±1), 15(±1), 20(±1), 30(±1), and 60(±5) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator and assessments of eyelid swelling, and tearing/watery eyes will be made by the subject at 10(±1), 15(±1), 20(±1), 30(±1), and 60(±5) minutes post-challenge (**Appendix 2**). If the subject fails to react positively [redacted] in both eyes in at least two out of the first three time points[5] within the first 20-minute interval, he/she will be excluded from the study.
- [redacted]
- *Scheduling of Next Visit (Visit 3):* Subjects will be asked to return to the office 2 weeks later for Visit 3.

10.3.1.3 VISIT 3 (Day 1): Enrollment/Randomization

- *Update of Medical/Medication History*
- *Visual Acuity Utilizing an ETDRS Chart:* The Investigator should be notified if there is a clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1.
- *Baseline -Ocular Allergic Signs and Symptoms Assessment:* [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 qualify to continue in the study will be randomly assigned to masked treatment using a 1:1:1 (ADX-102 ophthalmic drops [0.5%]: ADX-102 ophthalmic drops [0.1%]: vehicle of ADX-102 ophthalmic drops) assignment ratio. Subjects will be randomized by assignment of the lowest randomization number

[redacted]

available. Randomization will be stratified by average post-CAC itching scores [redacted]) at baseline (Visit 2). No numbers will be skipped or omitted.

- *Investigational Product Instillation:* [redacted].
- *Conjunctival Allergen Challenge (CAC)*: [redacted]
- *Post-CAC Ocular Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 10(±1), 15(±1), 20(±1), 30(±1), and 60(±5) minutes following allergen challenge. [redacted] 10(±1), 15(±1), 20(±1), 30(±1), and 60(±5) minutes post-challenge (**Appendix 2**).
- [redacted]
- *Adverse Event Query:* Adverse Events/Adverse Device Effects (both elicited and observed; expected and unexpected; suspected relationship to the treatment, suspected unrelated, and not related) will be monitored throughout the study. All adverse events (both elicited and observed) will be promptly reviewed by the Investigator for accuracy and completeness. All adverse events will be documented on the appropriate CRF.
- *Scheduling of Next Visit (Visit 4):* Subjects will be asked to return to the office approximately 2 weeks later for Visit 4, the Onset of Action CAC Visit.

10.3.1.4 VISIT 4 (Day 15±3): 10-Minutes Onset of Action CAC

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Urine Pregnancy Test (for females of childbearing potential)*
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event.
- *Pre-CAC Ocular Allergic Signs and Symptoms Assessment:* [redacted]

- *Slit Lamp Biomicroscopy*
- *Investigational Product Instillation:* [redacted]
- *Conjunctival Allergen Challenge*: [redacted]
- *Post-CAC Ocular Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 10(±1), 15(±1), 20(±1), 30(±1), and 60(±5) minutes following allergen challenge. [redacted] at 10(±1), 15(±1), 20(±1), 30(±1), and 60(±5) minutes post-challenge (**Appendix 2**).
- *Exit Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event.
- *Exit Slit Lamp Biomicroscopy*
- *IOP Measurement:* Intraocular Pressure (IOP) will be measured in each eye by contact tonometry. An IOP of ≥ 30 mmHg or an increase of 10 mmHg over baseline (Visit 1) will be considered an Adverse Event.
- *Dilated Fundoscopy*
- [redacted]
- *Adverse Event Query*
- *Study Exit*

If a female has a positive pregnancy test during the study, then the investigator will notify Ora immediately. The investigator will follow-up and document the outcome of the pregnancy and provide a copy of documentation to the Sponsor. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

10.4 SCHEDULE OF VISITS, MEASUREMENTS AND DOSING

10.4.1 Scheduled Visits

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

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

10.4.2 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 Utilizing an ETDRS chart
- Slit-lamp Biomicroscopy
- Intraocular Pressure
- Dilated Fundoscopy
- Assessment of Adverse Events

10.5 COMPLIANCE WITH PROTOCOL

Site staff will review concomitant medication use at each visit.

Subjects who are inappropriately enrolled will be discontinued from the study. The reason for such discontinuation will be recorded as “protocol violation” in the source document and on the appropriate page in the eCRF.

10.6 SUBJECT DISPOSITION

10.6.1 Completed Subjects

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

10.6.2 Discontinued Subjects

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

- adverse events
- protocol violations
- lack of efficacy
- administrative reasons (eg, inability to continue, lost to follow up)

- manifest clinically active signs or symptoms of allergic conjunctivitis during the pre-CAC ocular allergic signs & symptoms assessment at Visit 4
- 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 study Sponsor and will be clearly documented on the eCRF.

10.7 STUDY TERMINATION

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

10.8 STUDY DURATION

Four office visits over a period of approximately 5 weeks.

10.9 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 study drug 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, 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 giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

11 ADVERSE EVENTS

An 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) associated with medical device.

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 eCRF. 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 1 comprehensive event. Any pre-existing medical condition that worsens after administration of study medication will also be considered a new adverse event. Study medication includes the drug under evaluation or any other medications required by the protocol given during any stage of the study.

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.

11.1.1 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]

11.1.2 Relationship to Investigational Product

The relationship of each adverse event to the investigational product should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the investigational product caused the adverse event.

- *Not Suspected*: A reasonable possibility does not exist that the investigational product caused the adverse event.

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

11.1.3 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 Report of Prior Investigations (ROPI) or is not listed at the specificity or severity that has been observed.

- *Expected*: an AE that is listed in the IB or ROPI at the specificity and severity that has been observed.

- *Not applicable:* an AE unrelated to the IP.

AEs that are mentioned in the IB or ROPI 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.

11.2 SERIOUS ADVERSE EVENTS

An AE is considered serious if, in the view of either the investigator or Sponsor/designee, 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/designee, 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.

11.3 PROCEDURES FOR REPORTING ADVERSE EVENTS

All AEs and their outcomes must be reported to Ora, the study 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.

11.3.1 Reporting a Suspected Unexpected Adverse Reaction

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

11.3.2 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 case report form. 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 case report form. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must immediately notify the **appropriate contact in the Study Manual.**

In addition, the investigator must 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 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.

11.4 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 study subject prior to unmasking IP.

If the investigator determines that emergency unmasking is necessary, the investigator should identify the given subject's study 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.

Subjects will have the IP treatment discontinued immediately if treatment assignment is unmasked and will be discontinued from the study.

11.5 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 worsening or improvement expected by the Investigator)
- Event is otherwise explained, regardless of whether the subject is still participating in the study

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 adverse events identified on the last scheduled contact must be recorded on the AE CRF with the status noted.

12 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

12.1 STUDY POPULATIONS

12.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all subjects who are randomized. All data will be included and no subjects will be excluded because of protocol violations. The ITT population will be analyzed as randomized and will be used for the efficacy analyses.

12.1.2 Per-Protocol Population

The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 4 (Day 15) with no major protocol violations. This population will be analyzed as treated using observed data only for confirmatory analyses.

12.1.3 Safety Population

The safety population includes all randomized subjects who received the test article. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

12.2 GENERAL IMPUTATION METHODS

[redacted]

12.3 PRIMARY EFFICACY VARIABLES

The primary efficacy variable is:

- Ocular itching evaluated by the subject at 10(±1), 15(±1), and 20(±1) minutes post-CAC at Visits 3 and 4 (0-4 scale, allowing half unit increments).

12.4 CRITERIA FOR EFFICACY

This clinical study is designed to evaluate the efficacy of ADX-102 Ophthalmic Drops compared to vehicle in the prevention of ocular itching at each designated time point post-CAC at Visits 3 and 4.

To demonstrate the clinical effectiveness for ocular itching, ADX-102 Ophthalmic Drops will need to show clinical superiority over vehicle by at least 0.5 units of a 5 point scale for the 10(±1), 15(±1) and 20(±1) minutes post-CAC time points within a visit, and at least 1 unit for the majority [redacted] of the same three post-CAC time points within a visit for each treatment comparison. ADX-102 Ophthalmic Drops will also need to show statistical superiority over vehicle at each of the three time points. The treatments will be tested against vehicle hierarchically, with the higher dose (0.5% ADX-102 Ophthalmic Drops) tested first and the lower dose (0.1% ADX-102 Ophthalmic Drops) tested conditional upon the higher dose showing statistical significance over vehicle.

[redacted]

[redacted]

12.6 STATISTICAL HYPOTHESES

[redacted]

12.7 SAMPLE SIZE

[redacted]

12.8 DEMOGRAPHIC AND BASELINE MEDICAL HISTORY

The demographic and baseline medical history data will be summarized descriptively. For quantitative variables, the summaries will include the number of observations, mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

12.9 PRIMARY EFFICACY ANALYSES

The primary efficacy variable is measured at Visit 3 (1 hour post treatment) and Visit 4 (10-minutes post treatment). [redacted]

[redacted]

[redacted]

12.11 **ADJUSTMENT FOR MULTIPLICITY**

[redacted]

12.12 **SAFETY ANALYSIS**

The primary safety variable is the incidence of subjects with any adverse event during the entire study. The percentage of subjects with specific treatment-emergent adverse events (TEAEs) will be summarized for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Adverse events will also be summarized for treatment-related AEs, SAEs, by maximal severity, and by day of onset relative to the start of treatment.

The secondary safety variables of slit lamp biomicroscopy, dilated fundus examination, visual acuity, and IOP will be summarized descriptively using quantitative and qualitative

summary statistics as appropriate. Changes and shifts from baseline will also be summarized where applicable.

12.13 INTERIM ANALYSIS

No interim analyses are planned.

13 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 Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of investigational products in the countries involved will be adhered to.

13.1 PROTECTION OF HUMAN SUBJECTS

13.1.1 Subject Informed Consent

Informed consent 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.

All informed consent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB/IEC 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/IEC 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.

Informed consent may be obtained within 30 days prior to Visit 1, however, informed consent must be obtained prior to Visit 1 if any of the following criteria are determined during the telephone screening process:

- Proper washout of certain medications is necessary
- Sufficient time of discontinuation of contact lens wear is necessary
- Post-operative period

Medical/medication history, demographics, skin test and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).

13.1.2 Institutional Review Board (IRB) Approval

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

Only an IRB/ERC approved version of the ICF will be used.

13.2 ETHICAL CONDUCT OF THE STUDY

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

13.3 SUBJECT CONFIDENTIALITY

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the Sponsor, the IRB/IEC approving this study, the Food and Drug Administration, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

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

13.4 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 electrocardiograms. The investigator's copy of the eCRFs serves as the investigator's record of a subject's study-related data.

13.4.1 Retention of Documentation

All study related correspondence, subject records, ICFs, record of the distribution and use of all IPs and copies of eCRFs should be maintained on file for at least 2 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 2 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.

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

13.5.1 Labeling/Packaging

13.5.2 Storage of Investigational Product

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 study, in accordance with the conditions specified in this protocol.

13.5.3 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 and available for Sponsor's review during the course of the study.

13.5.4 Final accountability and Disposal of Investigational Product

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

13.6 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 eCRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

13.7 HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

13.8 PUBLICATIONS

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

14 REFERENCES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Day	**-21±3**	**-14±3**	**1**	**15±3**
PROCEDURE				
General Assessments				
Informed Consent & HIPAA[6]	X			
Demographic Data[1]	X			
Medical & Medication History[1]	X			
Update Medical & Medication History		X	X	X
Allergic Skin Test	X			
Urine Pregnancy Test	X			X
Randomization			X	
AE Assessment			X	X
Allergen Challenge				
CAC	X	X	X	X
[redacted]				
Relief Drop Instillation[7]	X	X	X	X
Visual/Systems Exams				
Visual Acuity Utilizing an ETDRS chart	X	X	X	X[8]
Slit Lamp Biomicroscopy	X	X	X	X[3]
Intraocular Pressure	X			X
Dilated Fundoscopy	X			X
Investigational Product				
IP Instillation			X[9]	X[10]
Exit from Study				X

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

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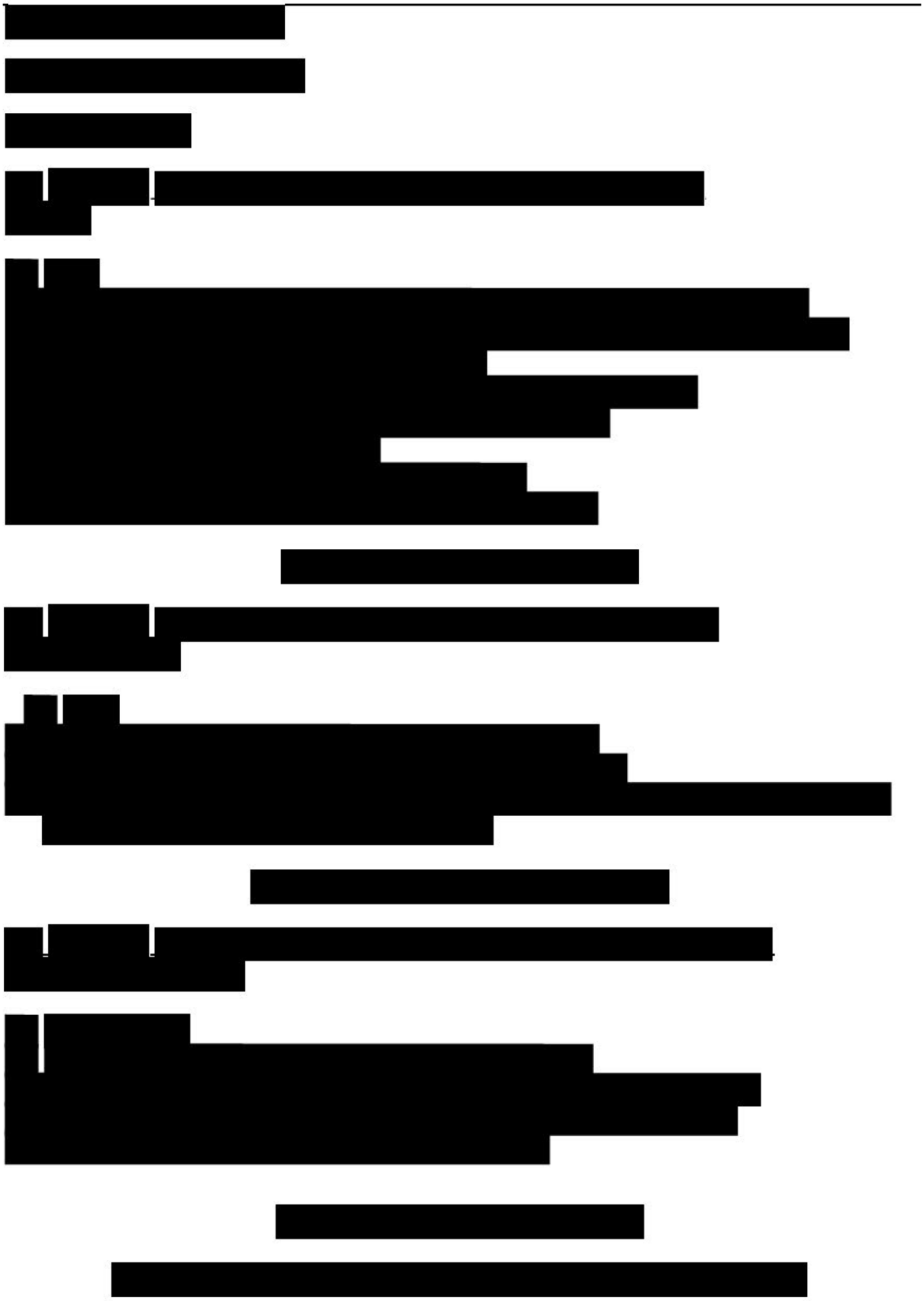

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APPENDIX 3: INVESTIGATIONAL PRODUCT COMPOSITION/ DESIGN

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APPENDIX 4: HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

APPENDIX 5: PROTOCOL AMENDMENT SUMMARY

Not Applicable.

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