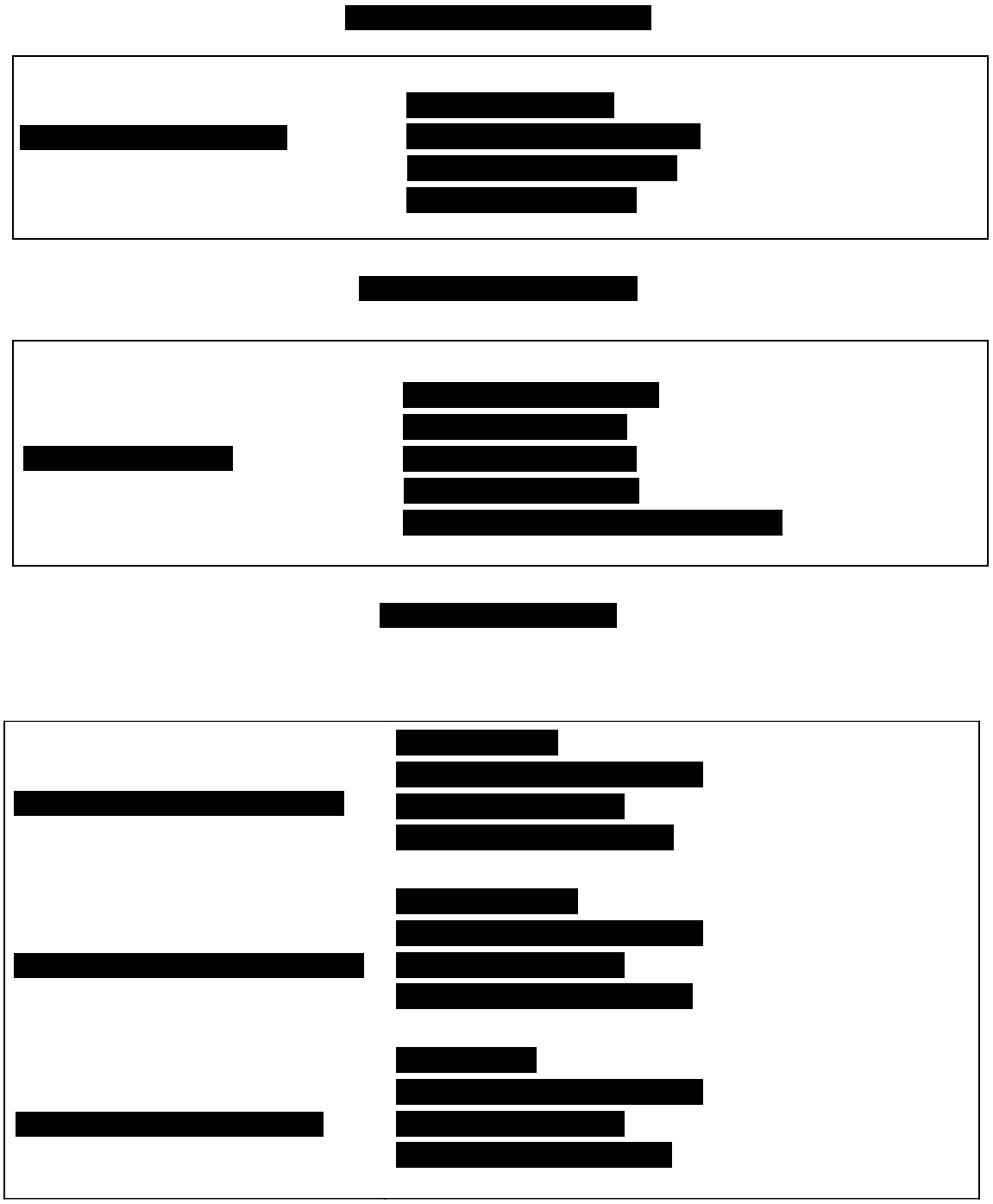
Clinical Trial Protocol

Protocol Title:	A Single-Center, Phase 2a, Randomized, Double-Masked, Clinical Study to Assess the Safety, Tolerability, and Pharmacodynamic Activity of ADX-102 Ophthalmic Solution in Subjects with Dry Eye Syndrome
Protocol Number:	ADX-102-DES-007
Study Phase:	2a
Product Name:	ADX-102 Ophthalmic Solution (0.5% and 0.1%)
[redacted]	[redacted]
Indication:	Dry Eye Syndrome (DES)
Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Ave. Lexington, MA 02421 USA
Contract Research Organization:	Ora. Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810 USA
[redacted]	[redacted]

	Date
Original Protocol:	27 March 2017

Confidentiality Statement



SYNOPSIS

Protocol Title:	A Single-Center, Phase 2a, Randomized, Double-Masked, Clinical Study to Assess the Safety, Tolerability, and Pharmacodynamic Activity of ADX-102 Ophthalmic Solution in Subjects with Dry Eye Syndrome
Protocol Number:	ADX-102-DES-007
Study Drug:	1) ADX-102 Ophthalmic Solution (0.5%) 2) ADX-102 Ophthalmic Solution (0.1%) 3) ADX-102 Ophthalmic Lipid Solution (0.5%)
Study Phase:	2a
Study Objective:	The objective of this study is to evaluate the safety, tolerability, and pharmacodynamic activity of ADX-102 Ophthalmic Solutions and ADX-102 Ophthalmic Lipid Solution in subjects with dry eye syndrome.
Overall Study Design	
Structure:	Single-center, double-masked, randomized study
Duration:	An individual subject's participation is estimated to be approximately 4 weeks (28 days).
Dosage/Dose Regimen:	Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally four times daily (QID) for 28 days (from Visit 1 to Visit 3). 1) ADX-102 Ophthalmic Solution (0.5%) 2) ADX-102 Ophthalmic Solution (0.1%) 3) ADX-102 Ophthalmic Lipid Solution (0.5%)
Summary of Visit Schedule:	3 visits over the course of approximately 4 weeks • Visit 1 = Day 1, Screening and Enrollment • Visit 2 = Day 8 ± 1, 1-Week Follow-Up • Visit 3 = Day 29 ± 2, 4-Week Follow-Up
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, double-masked study.
Study Population Characteristics	
Number of Subjects:	Approximately 60 subjects will be screened to enroll 45 subjects (15 per treatment arm).
Condition/Disease:	Dry Eye Syndrome (DES)

Inclusion Criteria:	**Subjects must:** 1. Be at least 18 years of age of either gender and any race; 2. Provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form; 3. Have a reported history of dry eye for at least [redacted] prior to Visit 1; 4. Have a history of use or desire to use eye drops for dry eye symptoms within [redacted] of Visit 1; 5. Report a score of [redacted] on the Ora Calibra® Ocular Discomfort & 4-symptom questionnaire in at least one symptom at Visit 1; 6. Have a Schirmer's Test score of [redacted] at Visit 1; 7. Have a tear film break-up time (TFBUT©) [redacted] at Visit 1; 8. Have a corneal fluorescein staining score of [redacted] in at least one region (e.g. inferior, superior, or central) at Visit 1; 9. Have a sum corneal fluorescein staining score of [redacted], based on the sum of the inferior, superior, and central regions, at Visit 1; 10. Have a total lissamine green conjunctival score of [redacted], based on the sum of the temporal and nasal regions at Visit 1; 11. Have at least one eye satisfy all criteria for 6, 7, 8, 9, and 10 above.
Exclusion Criteria:	**Subjects must not:** 1. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation, or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;

	2. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1; 3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study; 4. Have used any eye drops within 2 hours of Visit 1; 5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months; 6. Have used cyclosporine 0.05% or lifitigrast 5.0% ophthalmic solution within 45 days of Visit 1; 7. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within the last 6 months; 8. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1; 9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); 10. Have corrected visual acuity greater than or equal to logarithm of the minimum angle of resolution (logMAR) + 0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1; 11. Be a woman who is pregnant, nursing, or planning a pregnancy; 12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 3 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);

	13. Be a man or woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active males or females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, he/she must agree to use adequate birth control as defined above for the remainder of the study; 14. Have a known allergy and/or sensitivity to the test article or its components; 15. Have a condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study; 16. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; 17. Have previously used ADX-102 ophthalmic solution; 18. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1; 19. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.
Study Formulations:	• ADX-102 Ophthalmic Solution (0.5%) • ADX-102 Ophthalmic Solution (0.1%) • ADX-102 Ophthalmic Lipid Solution (0.5%)

Evaluation Criteria	
Safety Measures:	• Visual acuity • Slit-lamp evaluation • Adverse event query • Intraocular Pressure (IOP) • Undilated fundoscopy
Exploratory Pharmocodynamic Measures:	• Ora Calibra™ Drop Comfort assessment; [redacted]
Other:	Not applicable.

General Statistical Methods and Types of Analyses

Analysis Populations

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

[redacted]

Primary Efficacy Analyses:

There are no primary endpoints in this Phase 2a study.

Secondary Efficacy Analyses:

There are no secondary endpoints in this Phase 2a study.

Safety Variables:

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest relationship, and by system organ class, preferred term, maximal severity, and strongest relationship. Separate summaries will be performed for ocular and non-ocular AEs.

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

[redacted]

[redacted]

Summary of Known and Potential Risks and Benefits to Human Subjects

Refer to Investigator's Brochure.

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LIST OF ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
CFR	Code of Federal Regulations
CRF	case report form
DES	Dry Eye Syndrome
DHHS	Department of Health and Human Services
eCRF	electronic case report form
EKG	Electrocardiograph
ERC	ethical review committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	investigational new drug application
IOP	intraocular pressure
IRB	institutional/independent review board
ITT	intent-to-treat
IUD	Intra-uterine device
IWRS	interactive web response system
LASIK	laser *in situ* keratomileusis
LOCF	last observation carried forward
LPS	lipopolysaccharide
logMAR	logarithm of the minimum angle of resolution
MDA	Malondialdehyde; malonaldehyde
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
mL	Milliliter
mm	Millimeter
µg	microgram
µL	microliter
µm	Micrometer
mmHg	millimeters of mercury
OD	right eye
OS	left eye
[redacted]	[redacted]
OU	both eyes
OTC	over-the-counter
PP	per protocol
QID	four times a day
SAE	serious adverse event

[redacted]	[redacted]
TEAEs	treatment emergent adverse events
VA	visual acuity

1 INTRODUCTION

[redacted]

[redacted]

2 CLINICAL STUDIES OF ADX-102 OPHTHALMIC SOLUTION

[redacted]

[redacted]

3 STUDY OBJECTIVES

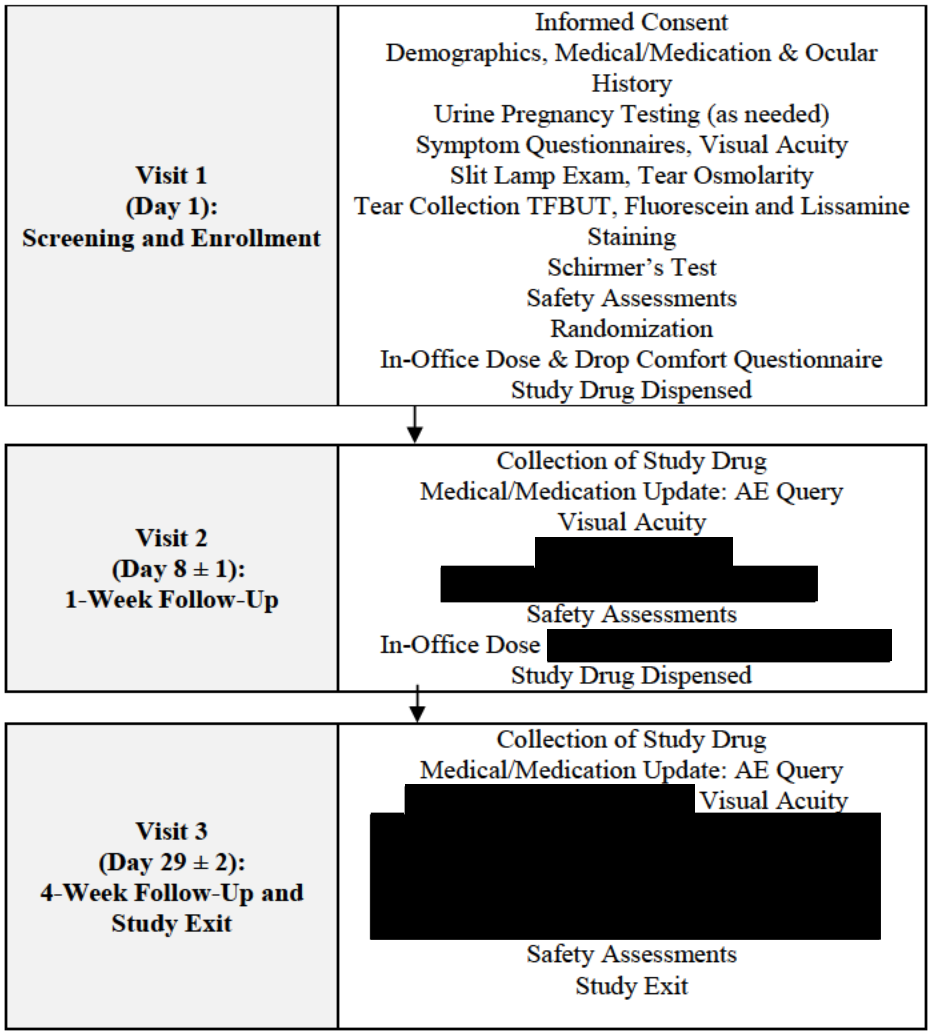
The objective of this study is to evaluate the safety, tolerability and pharmacodynamic activity of ADX-102 Ophthalmic Solutions (0.5% and 0.1%) and ADX-102 Ophthalmic Lipid Solution (0.5%) in subjects with dry eye.

CLINICAL HYPOTHESIS

[redacted]

4 DESIGN

This is a Phase 2a, single-center, randomized, double-masked study designed to evaluate the safety, tolerability and pharmacodynamic activity of ADX-102 Ophthalmic Solution (0.5%), ADX-102 Ophthalmic Solution (0.1%), and ADX-102 Ophthalmic Lipid Solution (0.5%) in subjects with dry eye. Approximately 45 male and female subjects at least 18 years of age with a subject-reported history of dry eye in both eyes and meeting all other study eligibility criteria will be randomized to receive treatment ADX-102 Ophthalmic Solution (0.5%), ADX-102 Ophthalmic Solution (0.1%), or ADX-102 Ophthalmic Lipid Solution (0.5%) in a 1:1:1 ratio (approximately 15 subjects in each treatment group).



Subjects who terminate early during the treatment period will be asked to complete safety assessments (as listed in Appendix 1) prior to commencement of any alternative dry eye therapy (if at all possible). Subjects who are terminated early from the study will not be replaced.

5 STUDY POPULATION

5.1 Number of Subjects

It is estimated that approximately 60 subjects will be screened to enroll approximately 45 randomized subjects (15 in each arm). Subjects will be randomized in a 1:1:1 ratio of ADX-102 Ophthalmic Solution (0.5%) to ADX-102 Ophthalmic Solution (0.1%) to ADX-102 Ophthalmic Lipid Solution (0.5%).

5.2 Study Population Characteristics

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

5.3 Inclusion Criteria

Subjects must:

1. Be at least 18 years of age of either gender and any race;
2. Provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form;
3. Have a reported history of dry eye for at least [redacted] prior to Visit 1;
4. Have a history of use or desire to use eye drops for dry eye symptoms within [redacted] of Visit 1;
5. Report a score of [redacted] on the Ora Calibra® Ocular Discomfort & 4-symptom questionnaire in at least one symptom at Visit 1;
6. Have a Schirmer's Test score of [redacted] at Visit 1;
7. Have a tear film break-up time (TFBUT©) [redacted] at Visit 1;
8. Have a corneal fluorescein staining score of [redacted] in at least one region (e.g. inferior, superior, or central) at Visit 1;
9. Have a sum corneal fluorescein staining score of [redacted] based on the sum of the inferior, superior, and central regions, at Visit 1;
10. Have a total lissamine green conjunctival score of [redacted] based on the sum of the temporal and nasal regions at Visit 1;
11. Have at least one eye satisfy all criteria for 6, 7, 8, 9, and 10 above.

5.4 Exclusion Criteria

Subjects must not:

1. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation, or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;

2. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;

3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study;

4. Have used any eye drops within 2 hours of Visit 1;

5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months;

6. Have used cyclosporine 0.05% or lifitigrast 5.0% ophthalmic solution within 45 days of Visit 1;

7. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within the last 6 months;

8. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;

9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study);

10. Have corrected visual acuity greater than or equal to logarithm of the minimum angle of resolution (logMAR) + 0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1;

11. Be a woman who is pregnant, nursing, or planning a pregnancy;

12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 3 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);

13. Be a man or woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active males or females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, he/she

must agree to use adequate birth control as defined above for the remainder of the study;

14. Have a known allergy and/or sensitivity to the test article or its components;

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

16. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;

17. Have previously used ADX-102 ophthalmic solution;

18. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1;

19. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

5.5 Withdrawal Criteria (if applicable)

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

Subjects may withdraw consent from the study at any time.

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

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Exploratory Pharmacodynamic Variables

The following exploratory endpoints will be tested:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Ora CalibraTM Ocular Discomfort Scale;

[redacted]

6.2 Safety Measures

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

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Formulations

Randomized Study Treatments

- ADX-102 Ophthalmic Solution (0.5%)
- ADX-102 Ophthalmic Solution (0.1%)
- ADX-102 Ophthalmic Lipid Solution (0.5%)

7.1.2 Dispensation Schedule

- At the end of Visit 1, qualified subjects will be randomized and the first dose of study drug will be administered in office. A supply of ADX-102 Ophthalmic Solution (0.5%), ADX-102 Ophthalmic Solution (0.1%), or ADX-102 Ophthalmic Lipid Solution (0.5%) will be dispensed for dosing QID.
- At the end of Visit 2, the unused vials from their Visit 1 kit will be re-dispensed to subjects, and a second kit for dosing through Visit 3 will also be dispensed.
- At Visits 2 and 3, remaining/used study drug will be collected from subjects for drug accountability.
- Subjects will be instructed to not use study drug on the day of visits (Visit 2 and 3) prior to the visit.

7.1.3 Instructions for Use

Subjects will be instructed to dose in each eye QID (morning, noon, afternoon, and in the evening before bed). [redacted]

7.2 Other Study Supplies

Other study supplies include urine pregnancy tests, [redacted]

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

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

8.1.2 Informed Consent

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

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the exclusion criteria (Section 5.4).

8.1.4 Procedures for Final Study Entry

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

8.1.5 Methods for Assignment to Treatment Groups

Prior to initiation of study drug (at Visit 1), each subject who qualifies for entry will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. If all inclusion and exclusion criteria are met at Visit 1, each qualifying subject will then be assigned a randomization number at the end of Visit 1.

A randomization schedule will be provided to the investigational site. The randomization schedule will use block randomization, such that there will be an approximate equal number of subjects assigned to each of the three treatment arms at the site. The site staff will dispense to the patient the study kit labeled with the corresponding randomization number. The randomization number will be recorded on the patient's source document and electronic case report form (eCRF). A new kit will be dispensed at Visit 2 based on the subject's randomization. The Sponsor, Investigators,

and study staff will be masked during the randomization process and throughout the study.

8.2 Concurrent Therapies

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

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

8.2.1 Prohibited Medications/Treatments

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

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.3 Examination Procedures

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

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

Visit 1 (Day 1): Screening & Enrollment

- Informed consent / HIPAA;
- Demographic data and medical / medication history;
- Review of qualification criteria;
- Urine pregnancy test (for females of childbearing potential);
- Ora Calibra® Ocular Discomfort;
- [redacted]
- Visual Acuity (ETDRS);
- Slit-lamp Biomicroscopy;
- [redacted]
- At least 20-minute wait;
- [redacted]

- Fluorescein staining – Ora Calibra®;
- Lissamine Green staining – Ora Calibra®;
- [redacted]
- [redacted]
- Intraocular Pressure;
- Undilated Fundoscopy;
- Adverse event query;
- Review of qualification criteria;
- Randomization & Dispensation of study drug kit according to randomization for QID dosing until Visit 2;
- [redacted]
- [redacted]
- Subjects will be instructed to dose in each eye four times daily (morning, noon, afternoon, and in the evening before bed);
    - Subjects will be instructed to dose in each eye before bed in the evening of Visit 2;
    - Subjects will be instructed to not dose with study drug on the morning of their next visit (Visit 2);
- Qualified subjects will be scheduled for Visit 2.

Visit 2 (Day 8 ± 1): 1-Week Follow-Up

- Collection and review of study drug;
- Subject will be asked if he/she dosed with study drug on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed;
- Medical/medication history update;
- Adverse event query;
- Ora Calibra® Ocular Discomfort;
- [redacted]
- [redacted]
- [redacted]
- Visual Acuity (ETDRS);
- Slit-lamp Biomicroscopy;
- [redacted]
- [redacted]
- Dispensation of study drug kits for QID dosing until Visit 3;
- [redacted]
- [redacted]

- Subjects will be instructed to dose in each eye four times daily (morning, noon, afternoon, and in the evening before bed);
    - Subjects will be instructed to dose in each eye before bed the evening of Visit 3;
    - Subjects will be instructed to not dose with study drug on the morning of their next visit (Visit 3);
- Subjects will be scheduled for Visit 3.

Visit 3 (Day 29 ± 2): 4-Week Follow-Up and Study Exit

- Collection and review of study drug;
- Subject will be asked if he/she dosed with study drug on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed;
- Medical/medication history update;
- Adverse event query;
- Urine pregnancy test (for females of childbearing potential);
- Ora Calibra® Ocular Discomfort;
- [redacted]
- Visual Acuity (ETDRS);
- [redacted]
- Intraocular Pressure;
- Undilated Fundoscopy;
- Adverse event query;
- Study Exit.

Early Termination/Discontinuation

If a subject is discontinued from the study prior to Visit 3 (Day 29 ± 2), then all safety evaluations that are to be performed at Visit 3 (Day 29 ± 2)

should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

Adverse Events (both elicited and observed) and serious adverse events (SAEs) will be monitored throughout the study. The investigator will promptly review all adverse events (both elicited and observed) for accuracy and completeness. All adverse events will be documented on the appropriate source document and case report form.

If a female reports a pregnancy or has a positive pregnancy test during the study the investigator will notify Ora 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. The pregnant subjects will be discontinued from the study as per the exclusion criteria.

8.4 Schedule of Visits, Measurements, and Dosing

8.4.1 Scheduled Visits

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

8.4.2 Unscheduled Visits

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

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit-lamp Biomicroscopy;
- Visual Acuity;
- Intraocular Pressure;
- Urine Pregnancy Test;
- Undilated Fundoscopy;
- Assessment of Adverse Events;
- Assessment of concurrent medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.5 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of study drug at the end of Visits 1 and 2, and given written instructions. The used and unused study drug

vials will be collected at each visit from Visit 2 up to and including Visit 3 to assess dosing and symptom assessment compliance. [redacted]

8.6 Subject Disposition

8.6.1 Completed Subjects

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

8.6.2 Discontinued Subjects

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

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

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

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.

Discontinued subjects will not be replaced.

8.7 Study Termination

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

8.8 Study Duration

An individual subject's participation will involve 3 visits over approximately a 4-week period (28 days).

8.9 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, subject safety, and

ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

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

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug will also be considered a new adverse event.

If there is a worsening of a medical condition that was present prior to the administration of the study drug, this should also be considered a new adverse event and reported. Any medical condition present prior to the administration of the study drug that remains unchanged or improved should not be recorded as an adverse event at subsequent visits.

Study drug includes the investigational drug under evaluation.

Documentation regarding the adverse event should be made as to the nature, date of onset, end date, severity, relationship to study drug, 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 adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by the investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

9.1.2 Relationship to Study Drug

The relationship of each adverse event to the investigational product should be determined by the investigator (in a blinded manner) using these explanations:

- *Definite:* When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and adverse event.
- *Probable:* When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable.
- *Possible:* When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example; due to missing data or insufficient evidence.
- *None:* When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- *Unclassified:* When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

9.1.3 Expectedness

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

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

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

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

9.2 Serious Adverse Events

An adverse event is considered serious if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;

  Note: An adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject

at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: A serious adverse event specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All adverse events and their outcomes must be reported to Ora, the study sponsor, and the institutional review board (IRB)/independent ethics committee (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

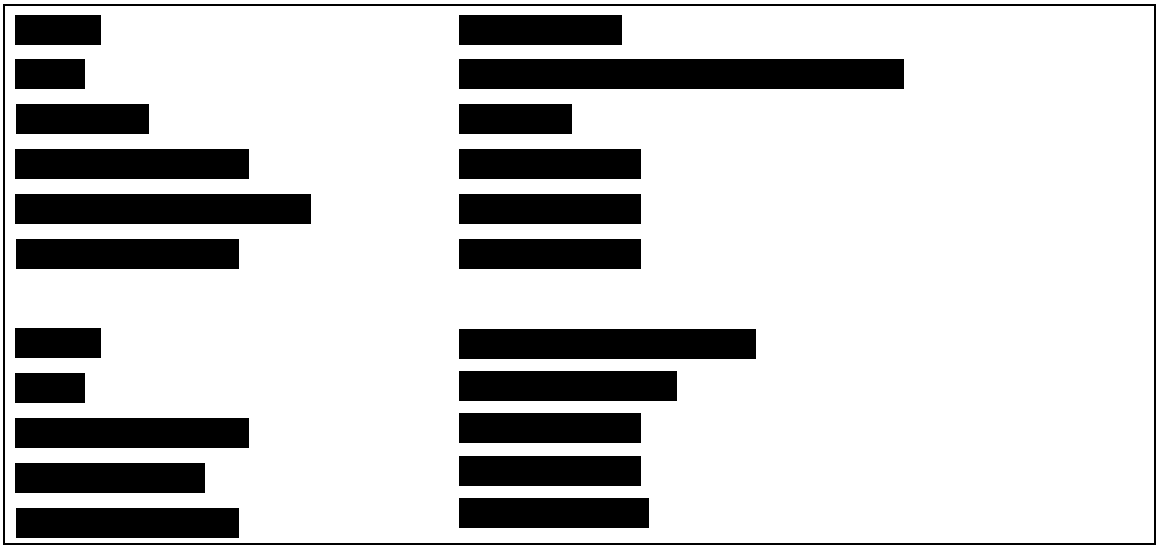
All adverse events that are 'suspected' and 'unexpected' are to be reported to Ora, the study sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

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

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

Contact information for reporting Serious Adverse Events:



9.4 Procedures for Unmasking of Study Drug

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking study drug. The unmasked subject will be discontinued from the study.

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

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

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

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis populations will be considered:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.

- Per-Protocol Population – The per-protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.

- Safety Population – The safety population includes all randomized subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

[redacted]

10.2 Statistical Hypotheses

This is a Phase 2a study to assess the safety, tolerability and pharmacodynamic activity of ADX-102 Ophthalmic Solution in subjects with dry eye syndrome. There are no primary endpoints and no formal statistical hypotheses.

10.3 Sample Size

[redacted]

10.4 Statistical Analysis

[redacted]

10.4.2 Unit of Analysis

[redacted]

10.4.3 Missing Data

[redacted]

10.4.4 Multiplicity Consideration

[redacted]

10.4.5 Primary Efficacy Analyses

There are no primary endpoints in this Phase 2a study.

10.4.6 Secondary Efficacy Analyses

There are no secondary endpoints in this Phase 2a study.

10.4.7 Safety Variables

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class and preferred term for treatment-related TEAEs; and by system organ class, preferred term, and study day of onset. Separate summaries will be performed for ocular and non-ocular AEs.

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

10.4.8 Exploratory Pharmacodynamic (Efficacy) Measures

[redacted]

[redacted]

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[redacted]

10.4.9 Interim Analyses

[redacted]

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

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

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent 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.

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

11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). The investigator must

obtain appropriate IRB approval before initiating the study and re-approval at least annually.

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

11.2 Ethical Conduct of the Study

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

11.3 Subject Confidentiality

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

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

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

11.4 Documentation

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

11.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all study drug and copies of case report forms should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by

an agreement with the sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

11.5.1 Labeling/Packaging

[redacted]

11.5.2 Storage of Study Drug

[redacted]

11.5.3 Accountability of Study Drug

[redacted]

11.5.4 Return or Disposal of Study Drug

[redacted]

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

All subject data will be captured in the subject source documents which will be transcribed in the eCRFs. The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a

manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

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

11.7 Handling of Biological Specimens

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11.8 Publications

[redacted]

12 REFERENCES

[redacted]

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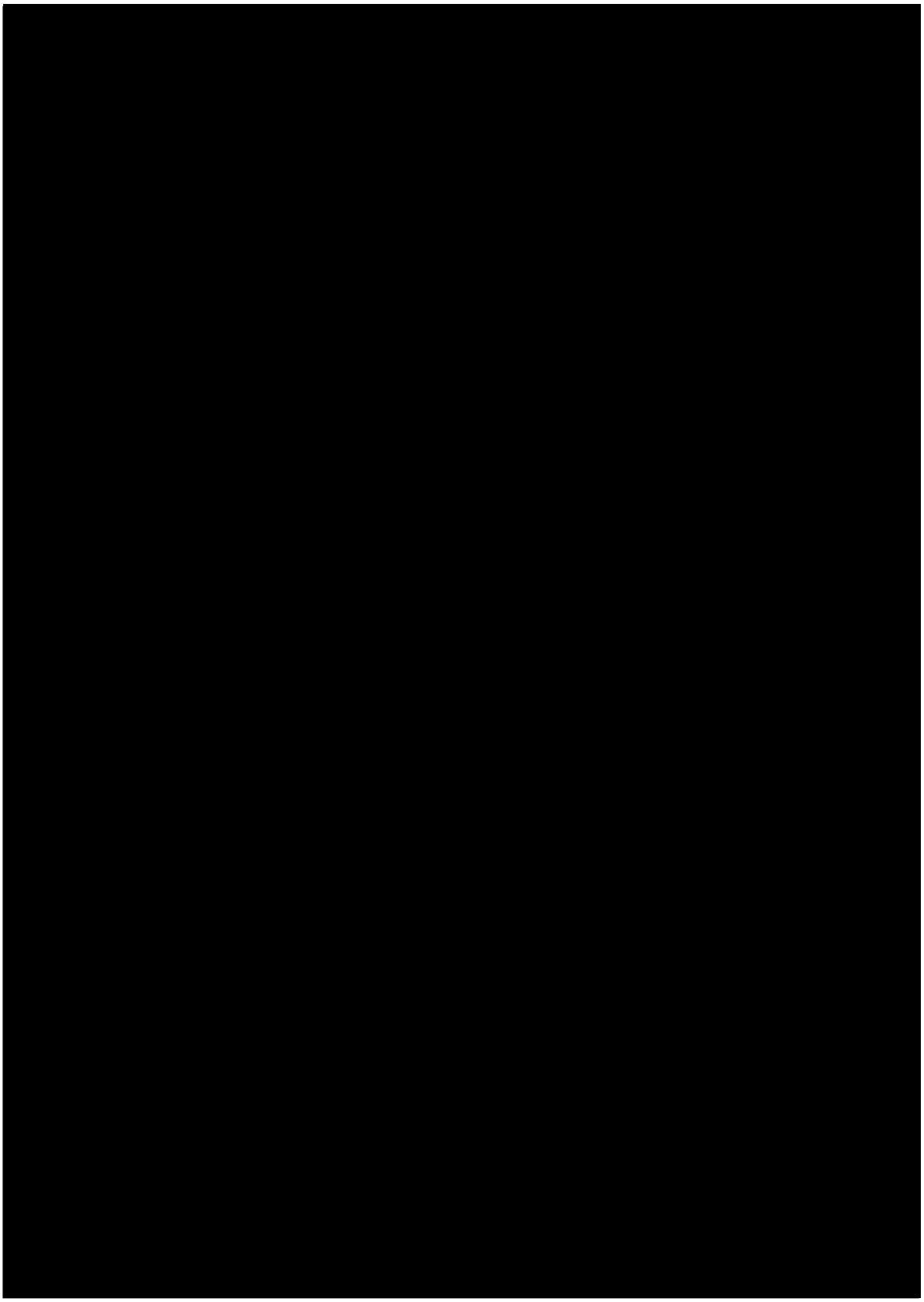
13 APPENDICES



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

Visual Acuity Procedures

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Ora Calibra® Ocular Discomfort Scale

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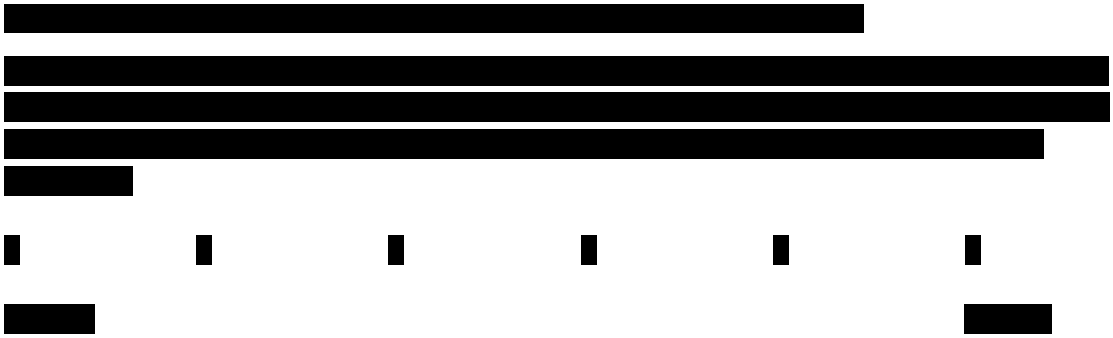

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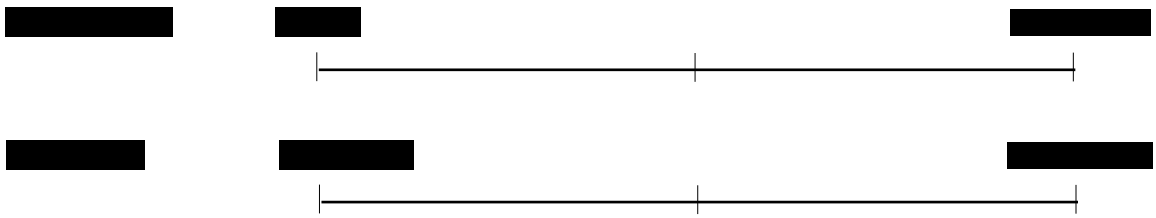

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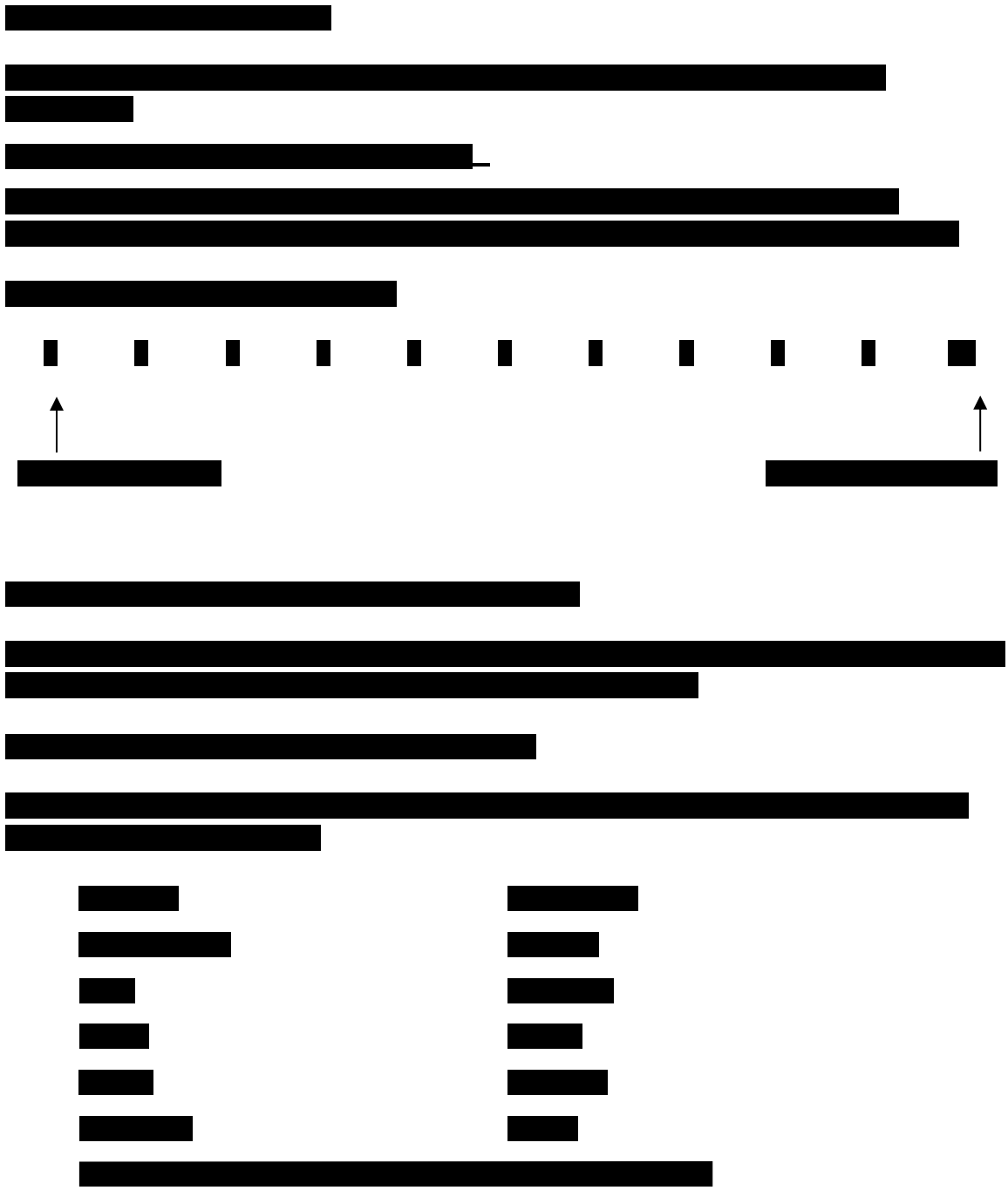
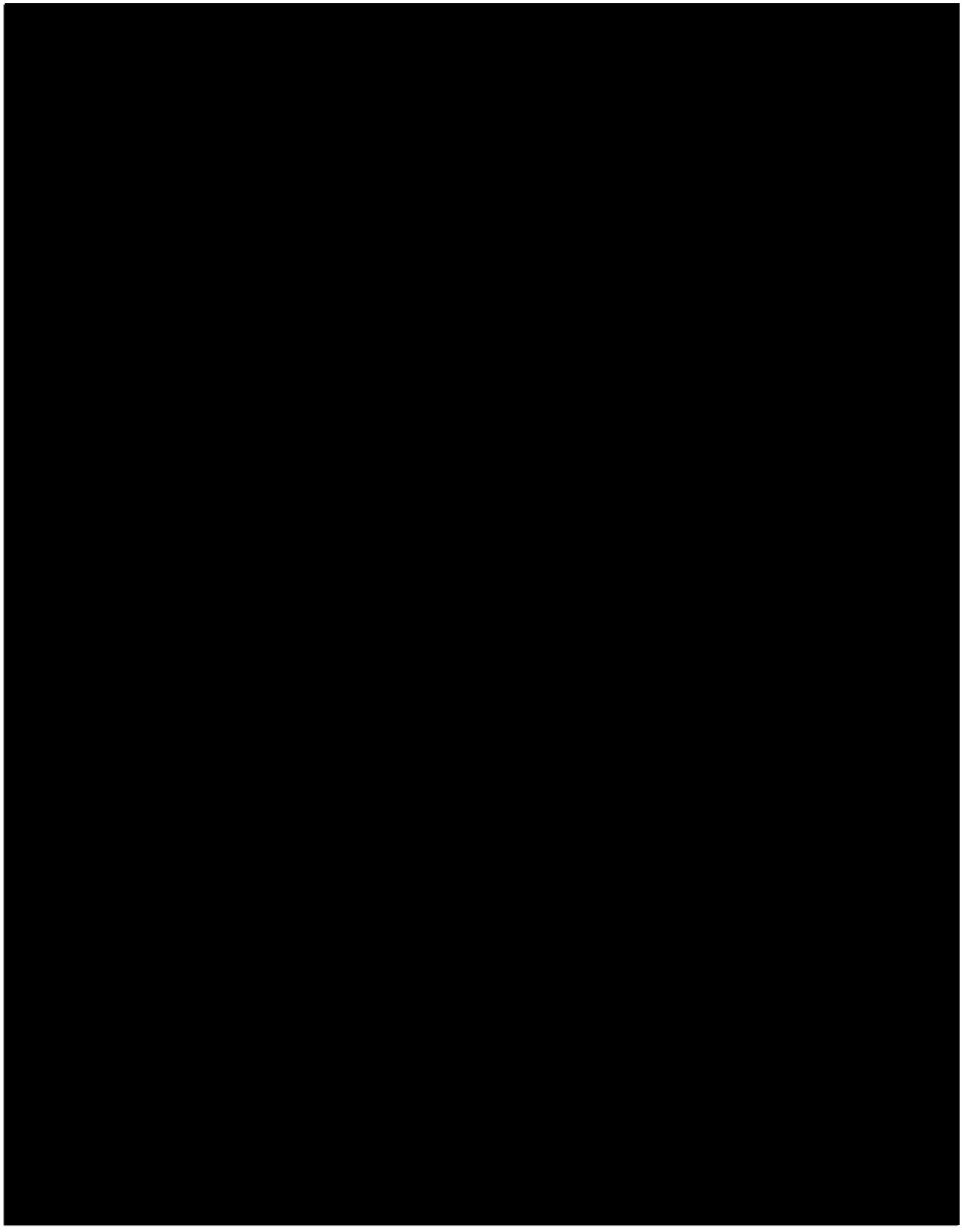


Appendix 3: Amendment Summary of Changes

Not applicable



Appendix 5: Investigator's Signature

Protocol Title: A Single-Center, Phase 2a, Randomized, Double-Masked, Clinical Study to Assess the Safety, Tolerability and Pharmacodynamic Activity of ADX-102 Ophthalmic Solution in Subjects with Dry Eye Syndrome

Protocol Number: ADX-102-DES-007

Final Date: 27 March 2017

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

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