A Phase 3b Open-Label Study Designed to Evaluate Tear Production Stimulated by 0.003% AR-15512

STUDY ID:

DEF512-E002

PROTOCOL v.2

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Clinical Trial Protocol: DEF512-E002

Protocol Title:	A Phase 3b Open-Label Study Designed to Evaluate Tear Production Stimulated by 0.003% AR-15512
Protocol Number:	DEF512-E002
Study Phase:	Phase 3b
Investigational Product Name:	AR-15512 ophthalmic solution 0.003%
IND Number:	147005
Indication:	Dry Eye Disease
Investigators:	Single-center
Sponsor:	Alcon Research, LLC and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099
Contract Research Organization:	Ora, Inc. 138 Haverhill Street Suite 102 Andover, MA 01810, U.S.A Phone: +1-978-685-8900

CONFIDENTIAL STATEMENT

1 SYNOPSIS

Protocol Title:	A Phase 3b Open-Label Study Designed to Evaluate Tear Production Stimulated by 0.003% AR-15512
Protocol Number:	DEF512-E002
Investigational Product:	AR-15512 ophthalmic solution 0.003%
Study Phase:	Phase 3b
Primary Objective(s):	Stage 1 and Stage 2: To evaluate tear production, via tear meniscus height (TMH) as measured by optical coherence tomography (OCT), following acute administration of AR-15512 ophthalmic solution 0.003% (hereafter 0.003% AR-15512) in subjects with dry eye disease (DED).
[redacted]	
Overall Study Design:	
Structure:	Single-center, open-label, single-arm, two-stage acute dosing
Duration:	This study will consist of 1 day at single visit (acute).
Dosage/Dose Regimen/ Instillation/Application/Use:	Qualified subjects will be dosed in clinic by site staff once at Visit 1 with 0.003% AR-15512 (1 drop in each eye) in a staggered cadence (left eye followed by dosing of the right eye approximately 2 - 4 hours after completion of post-drop OCT).
Summary of Visit Schedule:	The study consists of 1 Visit (Screening, Enrollment and Assessments).
Study Population Characteristics:	
Number of Subjects:	Approximately 80 subjects will be enrolled with approximately 40 subjects enrolled in Stage 1 and approximately 40 subjects in Stage 2

Condition/Disease:	Dry Eye Disease
Inclusion Criteria:	To be eligible to participate in either stage of this trial, an individual must meet all the following criteria: 1. Male or female, 18 years of age or older. 2. Within the last 12 months, have a previous history of DED, either clinician diagnosed, or patient reported. 3. Within the last 6 months, have used, or desired to use artificial tears for DED symptoms. 4. Within the last 6 months, have a documented Schirmer test with or without topical anesthesia score ≥ 2 and < 10 mm/5 min. 5. Have a total corneal sodium fluorescein staining score ≥ 1 and ≤ 15 based on the modified National Eye Institute (NEI) grading scheme, with no one region scoring > 3. 6. Have an Ocular Surface Disease Index (OSDI)© score > 12. 7. Corrected Visual Acuity (Snellen) 20/200 or better in both eyes. 8. Good general and ocular health, as determined by the investigator using medical history, ophthalmic examination and history. 9. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. 10. Written informed consent from the subject has been obtained prior to any study related procedures. 11. Able, as assessed by the investigator, and willing to follow study instructions.
Exclusion Criteria:	Subjects meeting any of the following criteria will be excluded from entry into either stage of the study: <u>Ophthalmic:</u> 1. Current evidence of other clinically significant ophthalmic disease other than dry eye (e.g., glaucoma or macular degeneration). **Note:** Blepharitis and/or Meibomian gland disease not requiring treatment are allowed. 2. Use of artificial tears within 2 hours of the Study Visit. 3. History of ocular surgery within 1 year of the Study Visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision).

	4. Current evidence of other significant ophthalmic disease requiring topical medication (e.g., glaucoma, ocular hypertension) or other ophthalmic disease which the investigator believes may interfere with study findings or interpretation. 5. History of corneal transplant in one or both eyes. 6. Diagnosis of recurrent, ongoing, or active ocular infection including, but not limited to herpes simplex or zoster, vaccinia, varicella, tuberculosis of the eye, acanthamoeba, or fungal disease. 7. Use of contact lenses in either eye within 7 days of the Study Visit. 8. Punctal or intracanalicular plug present in either eyelid within 14 days of the Study Visit. 9. Use of lid hygiene (all forms of lid care including lid wipes, scrubs and purposeful cleansing of lids with soap or medicated shampoos, etc.) or heat masks within 7 days of the Study Visit. 10. Use of lid heating therapy (i.e., LipiFlow®, iLUX®, TearCare®) or Meibomian gland probing/therapeutic expression within 3 months of the Study Visit. 11. Use of Intense Pulsed Light (IPL) therapy on eyelids within 3 months of the Study Visit. 12. Use of any topical ocular anti-inflammatory medications (e.g., ocular cyclosporine [Restasis®, Cequa™, Vevye™, generics], lifitegrast [Xiidra®]) or any other prescription ophthalmic product for DED (e.g., perfluorohexyloctane [Meibo™]), any topical ocular corticosteroid, or any non-steroidal-anti-inflammatory agents within 30 days of the Study Visit. 13. Use of topical ocular autologous serum within 30 days of the Study Visit. 14. Use of any other topical ocular drop (prescription or OTC, including artificial tears) within 2 hours of the Study Visit. 15. Use of Tyrvaya™ (varenicline solution, nasal spray 0.03mg) within 30 days of the Study Visit. 16. Use of medications for the treatment of severe DED and/or Meibomian gland disease such as oral pilocarpine, oral cevimeline, oral macrolides, oral tetracyclines, oral tetracycline derivatives, and oral retinoids within 30 days of the Study Visit. <u>General/Systemic:</u> 17. Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying

	(e.g., antihistamines or tricyclic antidepressants) within 14 days of the Study Visit. 18. Initiation, discontinuation, or change in dose of a systemic corticosteroid within 30 days of the Study Visit. **Note:** Non-ocular topically applied corticosteroids (including topical creams, nasal sprays and inhalers) are not applicable to this exclusion. 19. Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) within 60 days of the Study Visit. 20. Have received any vaccine within 3 days prior to the Study Visit. 21. Use of an investigational product or device within 30 days of the Study Visit. 22. At the Study Visit, at the investigator's discretion, have uncontrolled or severe: a. Systemic allergy b. Rhinitis or sinusitis 23. History or presence of significant systemic disease (i.e., cardiovascular, pulmonary, hepatic, renal, hematologic, immunologic). Significant is defined as any disease that, in the assessment of the Investigator, would put the safety of the subject at risk through participation, or would prevent or confound protocol-specified assessments (e.g., severe Sjögren's syndrome, severe rheumatoid arthritis, severe systemic lupus erythematosus, uncontrolled immunodeficiency disease, etc.). 24. Known allergies or sensitivity to the study interventions or study diagnostic agents. 25. Positive pregnancy test or currently breastfeeding. 26. The subject has a condition or is in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study. 
Study Formulations and Formulation Numbers:	AR-15512 ophthalmic solution 0.003%

Evaluation Criteria:	
Efficacy Measures and Endpoints:	Stage 1: Primary Endpoint: • Change from baseline (pre-drop compared to 3 minutes post-drop) in TMH as measured by OCT. [redacted] Stage 2: Primary Endpoint: • Change from baseline (pre-drop compared to 3 minutes post-drop) in TMH as measured by OCT. [redacted]
Safety Measures:	Stage 1 and Stage 2 • Corrected Visual Acuity • Slit-lamp biomicroscopy • Adverse Events (AE)

General Statistical Methods and Types of Analyses

Analysis Sets:

- Safety Analysis set: The safety analysis set will include all subjects who have received at least one dose of 0.003% AR-15512.
- Full Analysis Set (FAS): The FAS will include all subjects who have received at least one dose of 0.003% AR-15512 and have pre-drop and 3-minute post-drop TMH measurements.
- Per Protocol Set (PPS): The PPS will include all subjects who are part of the FAS and have no major protocol deviations that could potentially influence the primary efficacy endpoint.

Analyses supporting Primary Objective:

The primary analysis will assess the change from baseline (pre-drop compared to 3 minutes post-drop) in TMH using OCT. A paired t-test using the FAS will be performed to test the pre-drop and post-drop difference in TMH. Descriptive statistics such as the mean, standard deviation, minimum, and maximum, as well as 90% confidence intervals, will be reported for the observed and change from baseline results.

Statistical Hypotheses:

In Stage 1, the primary hypothesis will focus on the change from baseline in TMH (measured at 3-minute post-drop minus pre-drop measurement) on the FAS. The study will be considered successful if the null hypothesis, H_0: Mean Change from baseline in TMH = 0 is rejected in favor of the alternative hypothesis, H_A: Mean Change from baseline in TMH > 0, at the 5% (one-sided) significance level.

For Stage 2, the primary hypothesis will remain the same and be tested independently in the remaining 40 subjects, with no pooling of data or analyses between stages maintaining distinct results.

Safety Analysis:

The AEs will be collected and coded using the latest MedDRA version. Treatment-Emergent adverse events (TEAE) will be summarized using system organ class (SOC) and preferred terms (PT) based on the safety analysis set. Other safety parameters collected will be summarized. Data on AEs and other safety parameters from Stage 1 and Stage 2 will be pooled for analysis.

Stage 1 Analyses:

Stage 1: A completed analysis will be conducted on OCT-TMH [redacted] data after approximately 40 subjects have completed and exited from the study. This analysis, previously referred to as an interim analysis, will now be considered the final efficacy analysis for Stage 1. During this analysis period, study enrollment will be temporarily paused. The primary purpose of this analysis is to identify early trends in the data for administrative planning purposes. Results from the Stage 1 analysis will guide the decision to either continue or terminate the study. Stage 1 data will also provide pilot data, helping to inform the design of Stage 2 and ensuring appropriate power to meet its objectives. Detailed procedures for assessing this analysis will be outlined in the Statistical Analysis Plan (SAP), which will supersede the protocol in case of any discrepancies between the two documents regarding data analysis plans.

No interim analysis is planned for Stage 2.

Sample Size Determination:

Stage 1:

A sample size of 40 subjects provides at least 99% statistical power to detect a significant difference in mean change from baseline in TMH, at the 5% (one-sided) significance level, assuming standard deviation (SD) of 623 µm and mean change of 550 µm [redacted]

Stage 2:

As mentioned above, the primary objective of Stage 2 is to assess the change in TMH, assuming a 5% one-sided significance level. Based on the final analysis of Stage 1, a sample size of 40 subjects will provide at least 99% power to detect the observed mean difference of 520 µm (SD 515 µm) for the difference between post-drop and pre-drop measurements. [redacted]

Summary of Known and Potential Risks and Benefits to Human Subjects

AR-15512 is a TRPM8 receptor agonist. AR-15512 (FL-no. 16.123) has been used as a flavoring agent or adjuvant in the food industry for many years and is generally recognized as

safe for these purposes (USFDA/FEMA GRAS No. 4681) in or on human food products with no safety concerns at specified use levels (EU/EFSA 2014; WHO/JECFA No. 2079).

Based on available information including that from the completed AR-15512 non-clinical development program, data support that when delivered BID through topical ocular administration, 0.003% AR-15512 possess the appropriate pharmacologic profile with an acceptable margin-of-exposure (i.e., wide therapeutic index) to fully support the safe use of 0.003% AR-15512.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BID	Twice Daily
CRO	Clinical Research Organization
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
H_0	Null Hypothesis
H_A	Alternative Hypothesis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IEC	Independent Ethics Committee
IP	Investigational Product
IPL	Intense Pulsed Light
IRB	Institutional Review Board
LogMAR	Logarithmic Minimum Angle of Resolution
NCS	Not Clinically Significant
NEI	National Eye Institute
OCT	Optical Coherence Tomography
[redacted]	[redacted]
OSDI	Ocular Surface Disease Index
OTC	Over-the-Counter
PT	Preferred Terms
SAE	Serious Adverse Event

[redacted]	[redacted]
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Serious Adverse Reactions
TEAE	Treatment-Emergent adverse events
[redacted]	[redacted]
TMH	Tear Meniscus Height
TOST	Two One-Sided Tests
TRPM8	Transient Receptor Potential Melastatin 8
WOCBP	women of childbearing potential

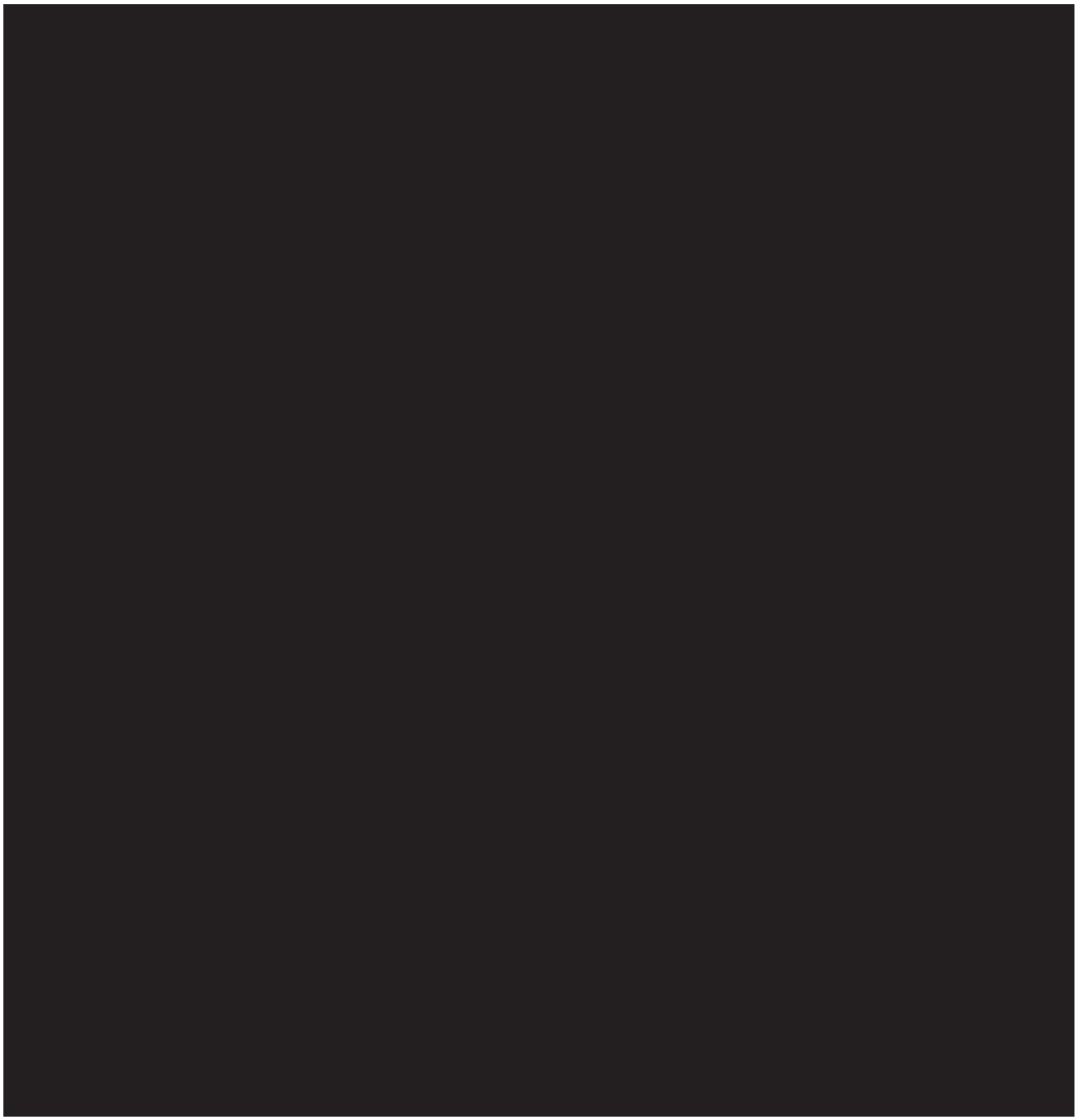
4 INTRODUCTION

4.1 Dry Eye Disease

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Craig, Nichols et al. 2017).

Despite the availability of several pharmaceutical products, there remains a significant unmet need for an effective topical ocular therapeutic to effectively treat the signs and symptoms of DED.

In recent years, increased attention has been placed on the neuronal regulation of tear production. AR-15512 is a potent and selective agonist of Transient Receptor Potential Melastatin 8 (TRPM8) that is being developed for the treatment of the signs and symptoms of DED. When applied topically to the eye, AR-15512 activates cold thermoreceptor nerve terminals of the cornea leading to regulation of tear production and blink rate. In addition, a cooling sensation may be produced that could be beneficial for reduction of ocular discomfort. Preclinical and clinical evidence to date support the mechanism of AR-15512 as an agonist of TRPM8 and the ability of AR-15512 to modulate corneal nerve impulse activity leading to increased tear production and a reduction of DED symptoms.



5 STUDY OBJECTIVES

5.1 Primary Objective(s)

- **Stage 1 and Stage 2:** To evaluate tear production, via tear meniscus height (TMH) as measured by Optical Coherence Tomography (OCT), following acute administration of 0.003% AR-15512 in subjects with DED.

6 CLINICAL HYPOTHESES

The clinical hypothesis for this study is that administration of 0.003% AR-15512 leads to an increase in tear production.

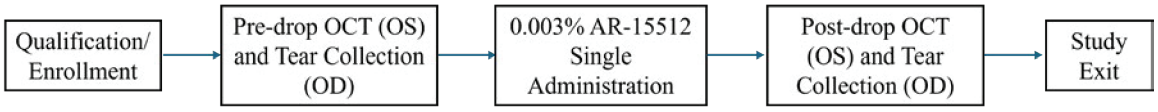
7 OVERALL STUDY DESIGN

This is a Phase 3b, single center, open-label, single-arm, two-stage, acute dosing study conducted in the United States.

Approximately 80 male and female subjects at least 18 years of age with a previous history of DED and meeting all study eligibility criteria will be enrolled. Enrollment will take place in two stages; with approximately 40 subjects being enrolled in each stage. While identical in design, the two stages of the study will be considered independent. Each of the stages will consist of 1 Visit (Screening, Enrollment, and Assessments). All subjects will be exited from the study at the end of the Study Visit. All qualified subjects post Screening will be dosed once in clinic by site staff with 0.003% AR-15512 in both eyes. The dosing will be in a staggered cadence, starting with the left eye followed by dosing of the right eye approximately 2 - 4 hours after completion of post-drop OCT. All subjects will undergo both baseline (pre-drop) and post-drop OCT imaging in the left eye and tear collection in the right eye at designated intervals. A study diagram is provided in Figure 1.

Details of assessments performed can be found in Appendix 1 (Schedule of Visits and Procedures) as well as the Manual of Procedures.

Figure 1 Study Design (Stage 1 and Stage 2)



8 STUDY POPULATION

8.1 Number of Subjects (approximate)

This study is anticipated to enroll approximately 40 subjects with DED into each stage. To achieve this goal, approximately 80 subjects may be screened for each of Stage 1 and Stage 2.

8.2 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.

8.3 Inclusion Criteria

To be eligible to participate in either stage of this trial, an individual must meet all the following criteria:

1. Male or female, 18 years of age or older.
2. Within the last 12 months, have a previous history of DED, either clinician diagnosed or patient reported.
3. Within the last 6 months, have used, or desired to use artificial tears for DED symptoms.
4. Within the last 6 months, have a documented Schirmer test with or without topical anesthesia score ≥ 2 and < 10 mm/5 min.
5. Have a total corneal sodium fluorescein staining score ≥ 1 and ≤ 15 based on the modified National Eye Institute (NEI) grading scheme, with no one region scoring > 3.
6. Have an Ocular Surface Disease Index (OSDI)© score > 12.
7. Corrected Visual Acuity (Snellen) 20/200 or better in both eyes Good general and

ocular health, as determined by the investigator using medical history, ophthalmic examination and history.

8. Good general and ocular health, as determined by the investigator using medical history, ophthalmic examination and history.

9. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

10. Written informed consent from the subject has been obtained prior to any study related procedures.

11. Able, as assessed by the investigator, and willing to follow study instructions.

8.4 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from entry into either stage of the study:

Ophthalmic:

1. Current evidence of other clinically significant ophthalmic disease other than dry eye (e.g., glaucoma or macular degeneration). Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed.

2. Use of artificial tears within 2 hours of the Study Visit.

3. History of ocular surgery within 1 year of the Study Visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision).

4. Current evidence of other significant ophthalmic disease requiring topical medication (e.g., glaucoma, ocular hypertension) or other ophthalmic disease which the investigator believes may interfere with study findings or interpretation.

5. History of corneal transplant in one or both eyes.

6. Diagnosis of recurrent, ongoing, or active ocular infection including, but not limited to herpes simplex or zoster, vaccinia, varicella, tuberculosis of the eye, acanthamoeba, or fungal disease.

7. Use of contact lenses in either eye within 7 days of the Study Visit.

8. Punctal or intracanalicular plug present in either eyelid within 14 days of the Study Visit.

9. Use of lid hygiene (all forms of lid care including lid wipes, scrubs and purposeful cleansing of lids with soap or medicated shampoos, etc.) or heat masks within 7 days of the Study Visit.

10. Use of lid heating therapy (i.e., LipiFlow®, iLUX®, TearCare®) or Meibomian gland probing/therapeutic expression within 3 months of the Study Visit.

11. Use of Intense Pulsed Light (IPL) therapy on eyelids within 3 months of the Study Visit.

12. Use of any topical ocular anti-inflammatory medications (e.g., ocular cyclosporine [Restasis®, Cequa™, Vevye™, generics], lifitegrast [Xiidra®]) or any other prescription ophthalmic product for DED (e.g., perfluorohexyloctane [Meibo™]), any topical ocular corticosteroid, or any non-steroidal-anti-inflammatory agents within 30 days of the Study Visit.

13. Use of topical ocular autologous serum within 30 days of the Study Visit.

14. Use of any other topical ocular drop (prescription or over-the-counter [OTC], including artificial tears) within 2 hours of the Study Visit.

15. Use of Tyrvaya™ (varenicline solution, nasal spray 0.03mg) within 30 days of the Study Visit.

16. Use of medications for the treatment of severe DED and/or Meibomian gland disease such as oral pilocarpine, oral cevimeline, oral macrolides, oral tetracyclines, oral tetracycline derivatives, and oral retinoids within 30 days of the Study Visit.

General/Systemic:

17. Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) within 14 days of the Study Visit.

18. Initiation, discontinuation, or change in dose of a systemic corticosteroid within 30 days of the Study Visit. Note: Non-ocular topically applied corticosteroids (including topical creams, nasal sprays and inhalers) are not applicable to this exclusion.

19. Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) within 60 days of the Study Visit.

20. Have received any vaccine within 3 days prior to the Study Visit.

21. Use of an investigational product or device within 30 days of the Study Visit.

22. At the Study Visit, at the investigator's discretion, have uncontrolled or severe:

    a. Systemic allergy

    b. Rhinitis or sinusitis

23. History or presence of significant systemic disease (i.e., cardiovascular, pulmonary, hepatic, renal, hematologic, immunologic). Significant is defined as any disease that, in the assessment of the Investigator, would put the safety of the subject at risk through participation, or would prevent or confound protocol-specified assessments (e.g., severe Sjögren's syndrome, severe rheumatoid arthritis, severe systemic lupus erythematosus, uncontrolled immunodeficiency disease, etc.).

24. Known allergies or sensitivity to the study interventions or study diagnostic agents.

25. Positive pregnancy test or currently breastfeeding.

26. The subject has a condition or is in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.

[redacted]

8.5 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.

The sponsor and/or investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 11.13.2).

9 STUDY PARAMETERS

9.1 Efficacy Measures and Endpoints

9.1.1 Primary Efficacy Measure(s)

Stage 1, the primary efficacy endpoint will be evaluated:

- Change from baseline (pre-drop compared to 3 minutes post-drop) in TMH as measured by OCT

Stage 2, the primary efficacy endpoint will be evaluated:

- Change from baseline (pre-drop compared to 3 minutes post-drop) in TMH as measured by OCT

[redacted]

[redacted]

9.2 Safety Measures (Stage 1 and Stage 2)

- Corrected Visual Acuity
- Slit-lamp biomicroscopy
- Adverse Events (AE)

10 STUDY MATERIALS

10.1 Study Treatment(s)

10.1.1 Study Treatment/Formulation

- AR-15512 ophthalmic solution 0.003%

10.1.2 Instructions for Use and Administration

AR-15512 Ophthalmic Solution 0.003%, administered once in clinic by site staff to both eyes (NOTE: the dosing will be in a staggered cadence; left eye followed by dosing of the right eye approximately 2 - 4 hours after completion of post-drop OCT).

Study intervention will be administered once only at the Study Visit. Details of dosing can be found in the Manual of Procedures.

10.2 Other Study Supplies

Details of other study supplies can be found in the Manual of Procedures.

11 STUDY METHODS AND PROCEDURES

11.1 Subject Entry Procedures

11.1.1 Overview

Subjects, as defined by the criteria in Sections 8.2, 8.3, and 8.4, will be considered for entry into this study.

11.1.2 Informed Consent

Written informed consent will be obtained from each subject. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The investigator is responsible for ensuring that no patient is subject to any study-related examination or activity before that patient has given informed consent. The patient must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the patient.

It should be emphasized that the patient is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact their subsequent care.

The investigator will inform the patient of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The patient must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the patient may be given time to reflect if this is required, or if the patient requests more time. Patients and/or legal guardian will be required to sign and date the informed consent form.

A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site. Signed informed consent must be attained prior to the conductance of any study procedures.

11.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in Exclusion Criteria (Section 8.4)

11.1.4 Procedures for Final Study Entry

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

11.1.5 Methods for Assignment to Treatment Groups

Each subject who signs an ICF will be assigned a screening number. Screening numbers will be assigned in sequential order at each site beginning with 001 and will follow the two-digit site number (e.g., subject 001 at Site 99 will have Screening Number 99-001). All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. Inclusion and exclusion criteria will be reviewed, and qualifying subjects will be enrolled into the study.

11.2 Demographics

Demographic data including age, sex, race, and ethnicity will be collected and recorded.

11.3 Medical and Surgical History

Significant medical and ophthalmic history will be collected and any current underlying medical/ophthalmic conditions, including those that may have resolved before the Study Visit, must also be recorded. All relevant medical and ophthalmic surgical procedures must be recorded.

11.4 Prior and Concomitant Medications

Any medication (including vaccines, OTC, prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of the Study Visit must be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken. Prior medications taken up to at least 30 days prior to the Study Visit must also be recorded.

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

11.4.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 8.4).

11.4.2 Escape Medications

No escape medications are required for this study.

11.4.3 Special Diet or Activities

No special diets or activities are required for this study.

11.5 Clinical Laboratory Tests

11.5.1 Pregnancy Testing

Urine pregnancy tests for women of childbearing are required. Pregnancy tests must be negative for the subject to receive study intervention.

An adult woman is considered to be of childbearing potential unless she is at least 1-year post-menopause (no menses for 12 months or more without an alternative medical cause) or at least 3 months post-surgical sterilization. Subjects must not intend to become pregnant during the study and must properly use an effective method of contraception.

11.6 Dispensing Study Intervention

Study intervention will be administered once only at the Study Visit. Details of dosing can be found in the Manual of Procedures.

11.7 Efficacy Assessment

11.7.1 OCT

Only the left eye of subjects will be imaged with OCT and this assessment should be performed by the Investigator, designated sub-Investigator or trained research personnel only. Details will be provided in the OCT Procedures Manual.

In brief, subject is seated in a comfortable position in front of the OCT. OCT imaging will occur:

a. Before 0.003% AR-15512 drop administration

b. 3 minutes ± 15 seconds after 0.003% AR-15512 drop administration

Images are recorded in the central plane of the lower eye lid, directly underneath the pupil.

11.8 Safety Assessments

11.8.1 Corrected Visual Acuity

Logarithmic minimum angle of resolution (LogMAR) visual acuity in both eyes must be assessed using an Early Treatment of Diabetic Retinopathy Study (ETDRS) Series 2000 chart. Visual acuity should be evaluated prior to ocular examinations as specified in the Schedule of Visits and Procedures (Appendix 1). Additional procedural details can be found in the Manual of Procedures.

11.8.2 Biomicroscopy

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the investigator) or not clinically significant (NCS). The following will be examined in both eyes:

- Eyelid
- Conjunctiva
- Cornea
- Anterior Chamber
- Iris
- Lens

Additional procedural details can be found in the Manual of Procedures.

11.9 Other Assessments

11.9.1 Ocular Surface Disease Index (OSDI)©

The OSDI© questionnaire consists of 12 questions regarding ocular symptoms, environmental triggers, and vision-related functioning in patients with DED (Schiffman,

Christianson et al. 2000). Additional procedural details can be found in the Manual of Procedures.

11.10 Examination Procedures

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

Details of examination procedures can be found in the Manual of Procedures.

11.11 Schedule of Visits, Measurements, and Dosing

11.11.1 Scheduled Visits

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

11.11.2 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."

11.12 Compliance with Protocol

A protocol deviation occurs when there is any non-adherence to a study procedure or schedule that is specified by the protocol. The term "protocol deviation" includes those departures from the protocol previously described by the term "protocol violation"; all departures from the protocol are now described as protocol deviations, regardless of the potential impact on subject safety. A Protocol Deviation Log shall be maintained by the site(s). Protocol deviations will be summarized in the final clinical study report.

11.13 Subject Disposition

11.13.1 Completed Subjects

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

11.13.2 Discontinued Subjects

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

- subject request/withdrawal
- AEs
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- sponsor termination of the 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 the sponsor and will be clearly documented on the CRF.

11.13.3 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened for eligibility up to one time if there is a reasonable possibility, in the

Investigator's opinion, that the patient might meet the eligibility criteria. It is encouraged for the investigator to discuss potential rescreening with the Sponsor. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

11.14 Study Termination

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

11.15 Study Duration

An individual subject's participation will involve 1 visit.

11.16 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 investigational product (IP) accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

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

11.17 Quality Tolerance Limits

Quality tolerance limits (QTLs) will be predefined through an internal risk management process and monitored on an ongoing basis, with documentation of QTLs that are met summarized in the clinical study report.

12 ADVERSE EVENTS

12.1 Performing Adverse Event Assessments

All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective eCRF.

Qualified study staff responsible for assessing AEs will be listed on the Site Authorization and Delegation Log. This includes assessment of AE severity and relationship to treatment. AE information may be volunteered by the subject or solicited by study personnel through non-leading questions.

Documentation of AEs/adverse reactions will include AE description, start date and stop date, severity, relationship, action(s) taken, seriousness, and outcome.

If a disease is known at the time an AE is reported, this diagnosis should be recorded rather than listing of individual symptoms. However, if a cluster of symptoms cannot be identified as a single diagnosis, each individual event should be reported separately. If a diagnosis is subsequently known, it should be reported as follow-up information.

When recording an AE, the following information should be provided on the study AE eCRF:

1. Action Taken with Study Intervention:
    - None
    - Study Intervention Discontinued
    - Study Intervention Interrupted
2. AE Outcome:
    - Fatal
    - Not Recovered/Not Resolved
    - Recovered/Resolved
    - Recovered/Resolved with sequelae
    - Recovering/Resolving

- Unknown/Lost to follow-up

12.2 Adverse Event Definitions

The following definitions of terms apply to this section:

- **Adverse event (AE):** any untoward medical occurrence associated with the administration of the study intervention in humans, whether or not considered to be related to the study intervention.

- **Adverse reaction (AR):** any AE for which there is a reasonable possibility that the administration of the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the administration of the drug and the AE.

    a) **Life-threatening AE or life-threatening AR:** an AE or AR is considered "life--threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or AR that, had it occurred in a more severe form, might have caused death.

    b) Serious adverse event (SAE) or serious adverse reaction (SAR): an AE or AR 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 or sight-threatening AE, subject hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as a serious adverse event when the hospitalization

or prolonged hospitalization was for an elective surgical procedure or for a preexisting condition (with no increase in severity).

- Unexpected AE or unexpected AR: an AE or AR is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

12.3 Reporting Adverse Events

AEs should be documented from the time the subject provides informed consent until subject participation in the study has been completed.

If an event occurs after informed consent but prior to subject enrollment and the commencement of study medication, it should be recorded as an AE. Any change in the health status after commencement of study medication should be recorded as TEAEs.

Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was diagnostic and the outcome was uneventful.

12.3.1 AEs and Prior Medical History

Any medical condition present prior to informed consent which remains unchanged or improved should not be recorded as an AE at subsequent visits. However, an AE should be recorded if the frequency, intensity, or the character of a pre-existing condition worsens during the study period beyond what would be expected from the natural progression of that condition.

Symptoms and signs that are consistent with the natural history of DED are not considered reportable adverse events. Such developments are recorded but are not reportable adverse events. Worsening of symptoms and signs of DED should be recorded as an AE or SAE only if judged by the investigator to have unexpectedly worsened in severity and/or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of DED, it is important to convey why the development was unexpected.

If there is a question as to whether a medical development should be reported as an adverse event, the Investigator is recommended to contact the Sponsor for guidance.

12.3.2 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:

- **Mild:** Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- **Moderate:** Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- **Severe:** Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

A change in increased severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to moderate, or from moderate to severe. In either case, the start and stop dates should be recorded.

Note: A severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations.

12.3.3 Relationship to Investigational Product

A relationship between the AE and the study intervention or study procedure will be determined by the Investigator, as applicable, for each AE using these explanations:

Not Related: The event is clearly related to other factors such as subject's clinical condition, therapeutic interventions, concomitant disease, or therapy administered to the subject and does not follow a known response pattern to the product, device, or procedure.

Unlikely Related: The event is most probably caused by other etiologies such as subject's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the product, device, or procedure.

Possibly Related: The event follows a reasonable, temporal sequence from the time of study medication administration or study procedure and/or follows a known response pattern to the product, device or procedure but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject.

Related: The event follows a reasonable, temporal sequence from the time of study medication administration or study procedure and/or follows a known response pattern to the product, device or procedure and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following study medication administration or procedure, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

12.3.4 Expectedness

- AEs or ARs are considered "unexpected" if they are not listed in the Reference Safety Information section of the IB for AR-15512 or are not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to AEs or ARs that are mentioned in the IB as occurring with this class of drugs or as anticipated from the pharmacological properties of AR-15512 and are not specifically mentioned as occurring with the study drug.

- For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or ARs that are mentioned in the IB 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.

- An Investigator must immediately (i.e., within 24 hours from time of awareness) report any SAE or SAR (see Section 12.2 for definitions) to the Sponsor or its clinical research organization (CRO) representative, whether or not considered drug-related, including those listed in the protocol or IB.

12.4 Serious Adverse Events, Serious Adverse Reactions or Suspected Unexpected Serious Adverse Reactions

12.4.1 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:

c) Death;

d) 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 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.

e) 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.

f) 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).

g) 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.

12.5 Procedure 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.

12.5.1 Reporting SAEs or SARs

An Investigator must immediately (i.e., within 24 hours) report any SAE or SAR (see Section 12.2 for definitions) to the Sponsor or its CRO representative, whether or not considered study intervention-related, including those listed in the protocol or IB. The Investigator must use the SAE report form and include an assessment of whether there is a reasonable possibility that the drug caused the event. The Investigator must report any SAE or SAR that occurs or is observed during the study. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form.

SAE reports will be evaluated by the Medical Monitor. Regulatory authorities, Institutional Review Board (IRB), and Investigators at each of the study sites will be informed as required.

12.5.2 Reporting Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Investigator must immediately (i.e., within 24 hours) report SUSARs. In the event of SUSAR, the site must notify the Medical Monitor for the study and submit an SAE report form and record the event within the Electronic Data Capture (EDC) system within 24 hours of notification, or occurrence of the SUSAR, whether or not complete information is available. In the case of incomplete information, the Investigator must provide follow-up information as soon as possible using the SAE report form.

12.5.3 SAE Report Contact Information

[redacted]

[redacted]

[redacted]

12.6 Procedures for Unmasking

This is an open-label study; masking procedures are not applicable.

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

The investigator will follow AE outcomes until study completion, the subject is considered lost to follow-up, or the AE is otherwise classified. The outcome of the AE at the time of study completion/lost to follow-up should be recorded in the AE eCRF. If the subject is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

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

12.8 Drug Technical Events and Device Deficiencies for Drug/Device Combination Products

Any technical events concerning the test article formulations or device deficiencies concerning the ophthalmic delivery device (i.e., blow-fill-seal) must be reported to the sponsor. The pharmacy manual provides instructions on how to report to the sponsor.

A drug technical event is a deficiency of any non-device constituents of the study intervention. Non-device constituents include the drug and drug excipients, packaging, information supplied by the manufacturer, and labelling related to the study intervention. Events may include inadequacies in quality, identity, safety, strength, purity, performance, and/or physical characteristics.

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

Do not use any study intervention suspected to have a drug technical event and/or device deficiency. Isolate the study intervention from other products in the same storage condition until follow-up communication and instructions are received from the sponsor.

A drug technical event or device deficiency may or may not be associated with subject harm. Adverse events, whether related or not related to technical events or device deficiencies, must be recorded in the adverse event eCRF.

13 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

13.1 Analysis Set

The following analysis population will be considered:

- Safety Analysis Set: The safety analysis set will include all subjects who have received at least one dose of 0.003% AR-15512.
- Full Analysis Set (FAS): The FAS will include all subjects who have received at least one dose of 0.003% AR-15512 and have pre-drop and 3-minute post-drop TMH measurements.
- Per Protocol Set (PPS): The PPS will include all subjects who are part of the FAS and have no major protocol deviations that could potentially influence the primary efficacy endpoint.

13.2 Statistical Hypotheses and Analyses Supporting Key Study Objectives

13.2.1 Stage 1

The primary hypothesis, for Stage 1, will focus on the change from baseline in TMH (measured at 3-minute post-drop minus pre-drop measurement) on the FAS. The primary efficacy hypotheses are as follows:

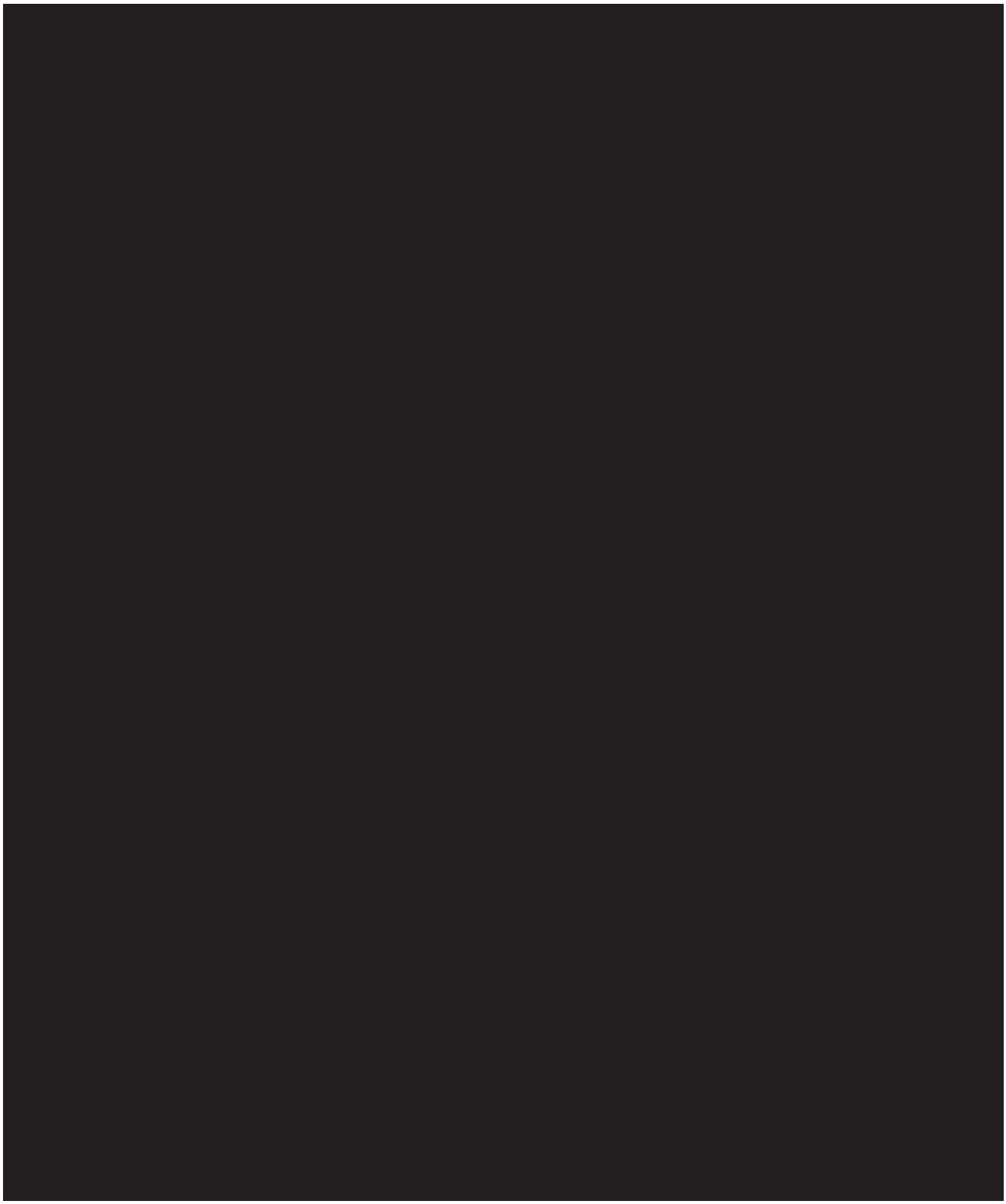
H_0: Mean change from baseline in TMH = 0

H_A: Mean change from baseline in TMH > 0

The study will be considered successful if the null hypothesis (H_0) is rejected in favor of the alternative hypothesis (H_A) at the 5% (one-sided) significance level.

The primary analysis will assess the change from baseline (pre-drop compared to 3 minutes post-drop) in TMH using OCT. A paired t-test using the FAS will be

performed to test the pre-drop and post-drop difference in TMH. Descriptive statistics such as the mean, standard deviation, minimum, and maximum, as well as 90% confidence intervals, will be reported for the observed and change from baseline results.



[redacted]

13.2.2 Stage 2

Following the final analysis of Stage 1, early trends in the data were identified to support subsequent planning. Results from this final analysis have guided the transition from Stage 1 to Stage 2.

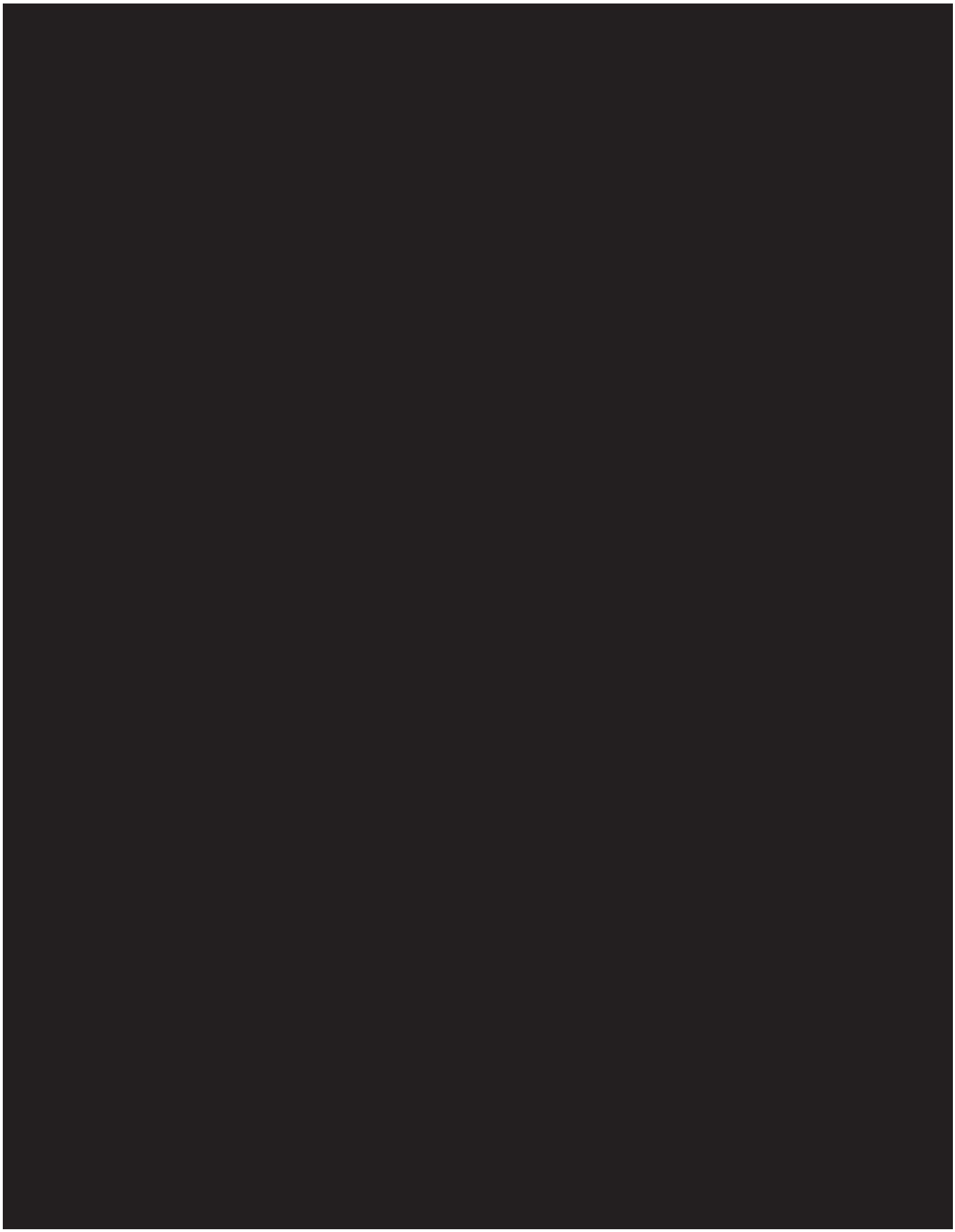
The primary hypothesis, for Stage 2, as in Stage 1 but analyzed independently, will focus on the change from baseline in TMH (measured at 3-minute post-drop minus pre-drop measurement) on the FAS. The primary efficacy hypotheses are as follows:

H_0: Mean change from baseline in TMH = 0

H_A: Mean change from baseline in TMH > 0

The study will be considered successful if the null hypothesis (H_0) is rejected in favor of the alternative hypothesis (H_A) at the 5% (one-sided) significance level.

[redacted]



[redacted]

13.4 Safety Analysis

Adverse events will be collected and coded using the latest MedDRA version. Treatment-emergent adverse events will be summarized using system organ class (SOC) and preferred terms (PT) based on the safety analysis set. Other safety parameters collected will also be summarized. Data on AEs and other safety parameters from Stage 1 and Stage 2 will be pooled for analysis, as the study design remains consistent across both stages. No formal inferential testing will be performed for safety outcomes.

13.5 Sample Size Determination

Stage 1: A sample size of 40 subjects provides at least 99% statistical power to detect a significant difference in mean change from baseline in TMH, at the 5% (one-sided) significance level. [redacted]

[redacted]

[redacted]

Stage 2: The primary objective of Stage 2 is to assess the change in TMH, assuming a 5% (one-sided significance). A sample size of 40 subjects will provide at least 99% power to detect the observed mean difference of 520 µm (SD 515 µm) for the difference between post-drop vs pre-drop measurements as identified in Stage 1. [redacted]

[redacted]

13.6 Interim Analyses

An interim analysis, in Stage 1, for futility (now called final analysis for Stage 1) will be performed on OCT-TMH [redacted] data after approximately 40 subjects have completed and exited from the study. During the interim analysis period, study enrollment will be temporarily paused. The primary purpose of the interim analysis is to identify early trends in the data for administrative planning purposes. Results from the planned futility analysis will guide the decision to either continue or terminate the study. Stage 1 data will also serve as pilot data for Stage 2, helping to inform its design. Detailed procedures for assessing futility will be outlined SAP, which will supersede the protocol in case of any discrepancies between the two documents regarding data analysis plans. There will be no interim analysis in Stage 2.

14 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 IP in the countries involved will be adhered to.

14.1 Protection of Human Subjects

14.1.1 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/Independent Ethics Committee (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 sponsor and provided in writing by Ora and/or sponsor prior to the consent process.

14.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations [CFR] Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

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

14.2 Ethical Conduct of the Study

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

14.3 Subject Confidentiality

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

Monitors, auditors, and other authorized representatives of Ora, the sponsor, the IRB/IEC approving this study, the 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 subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

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

14.4 Documentation

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

14.4.1 Retention of Documentation

All study-related correspondence, subject records, consent forms, records of the distribution and use of all IP, and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

14.5.1 Labeling/Packaging

Investigational product will be packaged and labeled into clinical kits. All clinical kits will be labeled according to applicable regulatory requirements.

14.5.2 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. The IP should be stored as directed on the investigational label and should be refrigerated at a controlled temperature (2 to 8°C / 36 to 46°F) until dispensed to subject. See more details in the Pharmacy Manual.

14.5.3 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, the amount of IP returned to the investigator by the subjects, and the amount returned or disposed of upon the completion of the study. A detailed inventory must be completed for the IP.

14.5.4 Return or Disposal of Investigational Product

When the study is completed or is terminated by the Sponsor, all study materials including used and unused study intervention kits / vials will be returned to the Sponsor or their designee. All study intervention accounting procedures must be completed before the study is considered to be concluded. The responsible person(s) at the Investigator's site has the sole responsibility to account for all used, partially used, and unused study intervention. This site staff member at the Investigator's site will complete a study intervention returns form or equivalent that will be signed by the Investigator or designee prior to returning the used and unused study intervention vials to the Sponsor or their designee.

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

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

14.7 Handling of Biological Specimens

Please refer to Appendix 2 Handling of Biological Specimens

14.8 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 sponsor will have the final decision regarding the manuscript and publication.

15 REFERENCES

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Schiffman, R. M., M. D. Christianson, G. Jacobsen, J. D. Hirsch and B. L. Reis (2000). "Reliability and validity of the Ocular Surface Disease Index." Arch Ophthalmol **118**(5): 615-621.

Schuirmann, D. J. (1987). "A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability." J Pharmacokinet Biopharm **15**(6): 657-680.

16 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND PROCEDURES (STAGE 1 AND STAGE 2)

Assessment	
Informed consent	X
Demographics	X
Medical, ophthalmic, and surgical history	X
Prior or concomitant medication review	X
Urine pregnancy test (WOCBP only)	X
OSDI© Questionnaire	X
Corrected visual acuity	X
Slit lamp biomicroscopy	X
Fluorescein staining of cornea (modified NEI grading scale)	X
Inclusion and exclusion criteria review	X
Study Enrollment	X
OCT and Tear Production Assessments[1]	X
Adverse events review	X
Corrected visual acuity	X
Slit lamp biomicroscopy	X
Study Exit	X

Abbreviations: NEI = National Eye Institute; OSDI© = Ocular Surface Disease Index©; OCT = optical coherence tomography; WOCBP = women of childbearing potential

[1] See details in the Manual of Procedures.

APPENDIX 2: HANDLING OF BIOLOGICAL SPECIMENS

Instructions for the handling of biological specimen will be provided in a separate laboratory manual.