A Phase 3b Study to Investigate the Effect of 0.003% AR-15512 on the Ocular Surface Characteristics of Subjects with Dry Eye Disease

STUDY ID

DEF512-E003

PROTOCOL v 3.0

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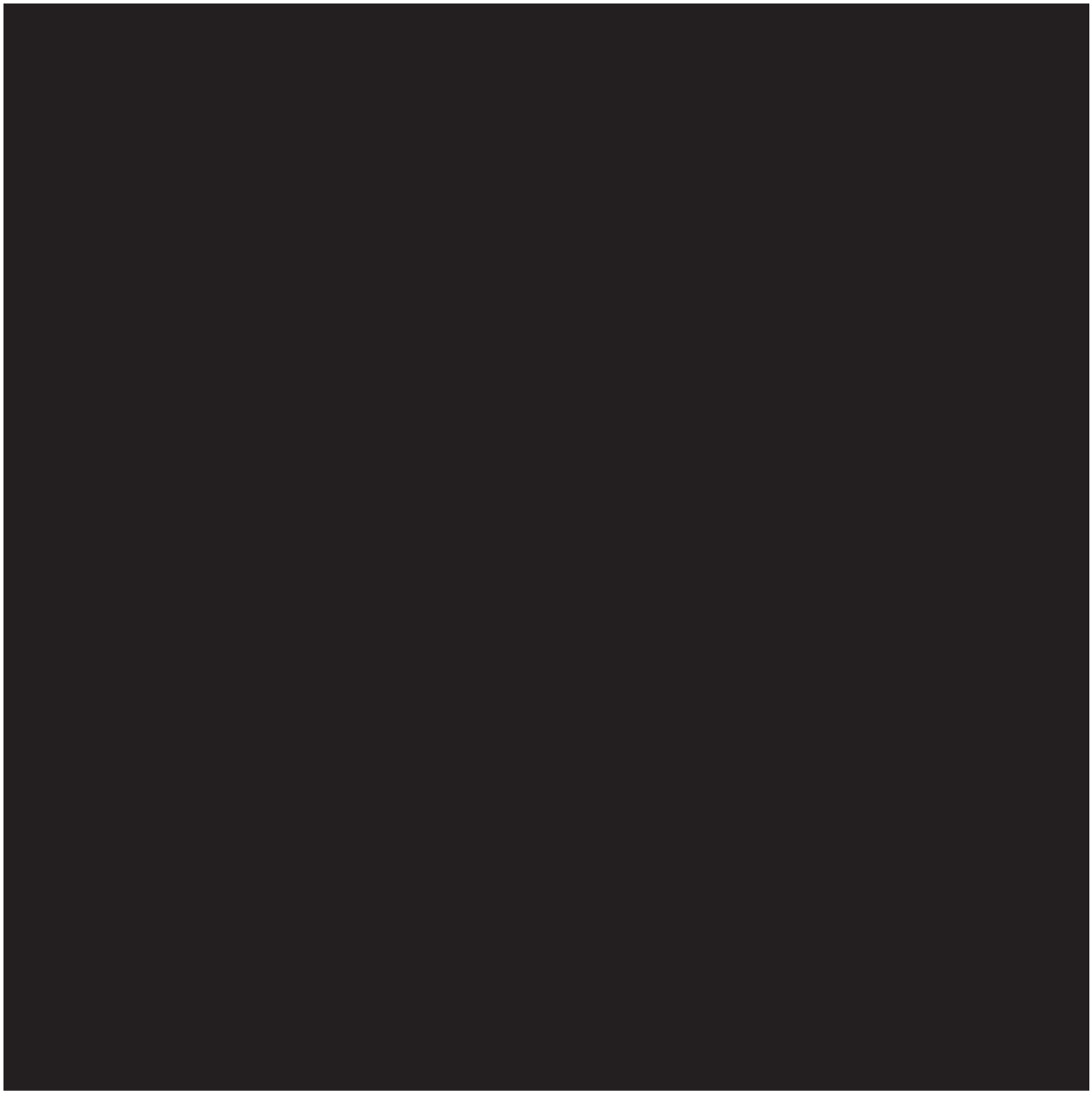
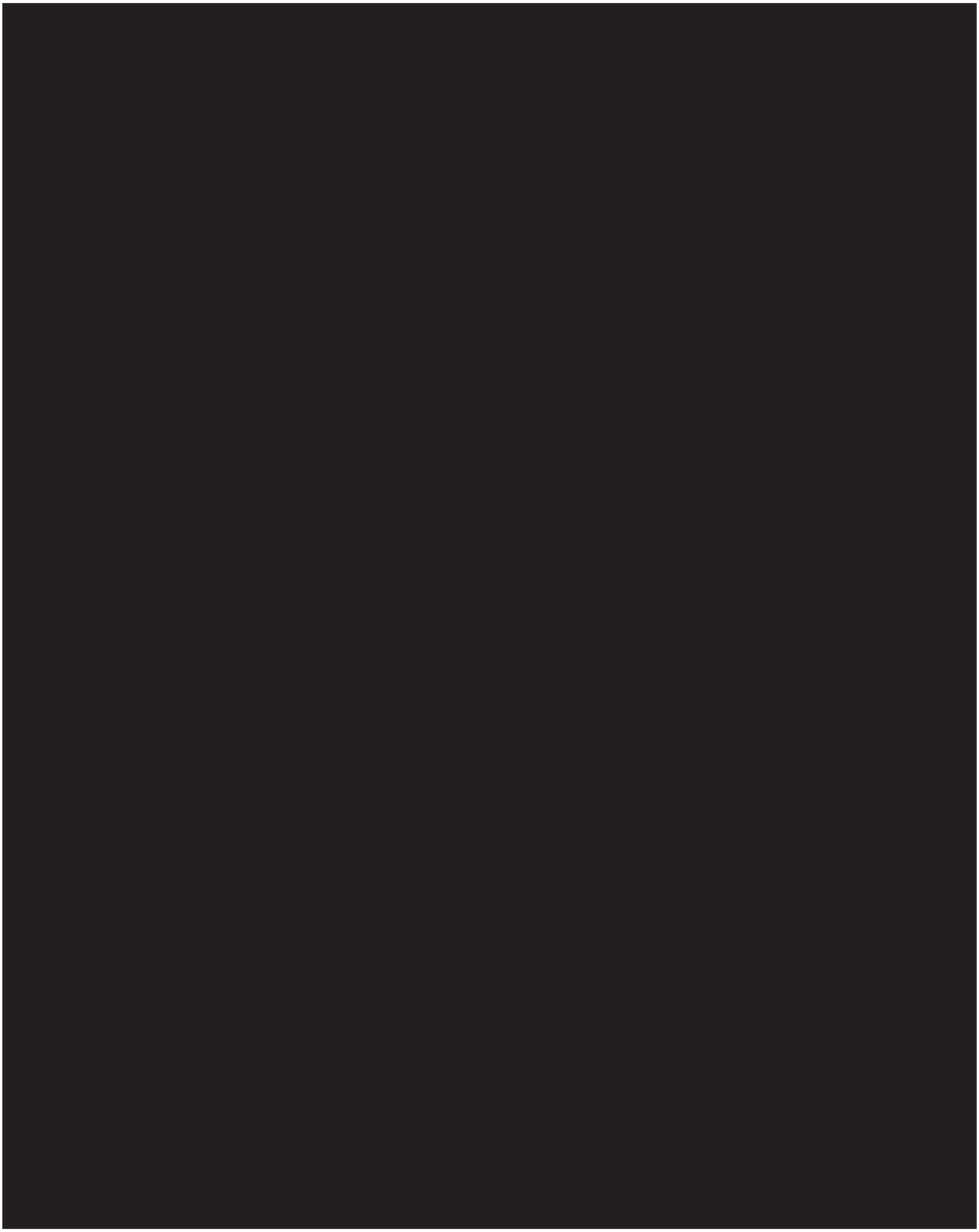
Clinical Trial Protocol: DEF512-E003

Protocol Title:	A Phase 3b Study to Investigate the Effect of 0.003% AR-15512 on the Ocular Surface Characteristics of Subjects with Dry Eye Disease
Protocol Number:	DEF512-E003
Study Phase:	Phase 3b
Investigational Product Name:	AR-15512 ophthalmic solution 0.003%
IND Number:	147005
Indication:	Dry Eye Disease
Investigators:	Multi-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 Study to Investigate the Effect of 0.003% AR-15512 on the Ocular Surface Characteristics of Subjects with Dry Eye Disease
Protocol Number:	DEF512-E003
Investigational Product:	AR-15512 ophthalmic solution 0.003%
Study Phase:	Phase 3b
Objective(s):	To evaluate the effect of AR-15512 ophthalmic solution 0.003% (hereafter 0.003% AR-15512) on ocular surface characteristics of subjects with dry eye disease (DED).
Overall Study Design:	
Structure:	Multi-center, comparator-controlled, double-masked, randomized, parallel group
Duration:	Approximately 15 weeks (2 weeks of run-in phase followed by 13-week randomized treatment period).
Dosage/Dose Regimen/ Instillation/Application/Use:	**Run-In Phase:** Subjects that qualify at the Screening visit will enter a 14-day run-in period where they will receive Artificial Tears (REFRESH® Classic) to be administered as one drop in each eye, twice daily (BID). **Treatment Phase:** Subjects that re-qualify at the Baseline visit (Day 1), will be randomized (1:1) to receive one of the following treatments to be administered as one drop in each eye BID for 90 days: • 0.003% AR-15512 • Artificial Tears (REFRESH® Classic)
Summary of Visit Schedule:	The study consists of 5 site Visits and 3 telephone calls over the course of approximately 15 weeks: • Visit 1 = Day -14 + 3, Screening • Visit 2 = Day 1, Baseline • Day 7 ± 3 Compliance Check Phone Call • Visit 3 = Day 30 ± 3, Follow-up • Day 45 ± 3, Compliance Check Phone Call • Visit 4 = Day 60 ± 3, Follow-up • Day 75 ± 3, Compliance Check Phone Call • Visit 5 = Day 90 ± 3, Follow-up, Study Exit
Measures Taken to Reduce Bias:	This is randomized (1:1), double masked study.
Study Population Characteristics:	
Number of Subjects:	Approximately 70 subjects will be enrolled.

Condition/Disease:	Dry Eye Disease
Inclusion Criteria:	To be eligible to participate in this trial, an individual must meet all the following criteria: 1. Male or female, 18 years of age or older at the Screening visit. 2. Have a previous history of DED, clinician diagnosed or patient reported, within the previous 6 months prior to the Screening visit. 3. Have used artificial tears for DED symptoms within 2 months prior to the Screening visit. 4. Both of the following signs in the same eye at both the Screening and Baseline visits and the same eye must qualify at both visits: a. Total ocular staining score ≥ 10 and ≤ 33 based on the modified National Eye Institute (NEI) grading scheme, with no one region scoring > 3. b. Total lissamine green staining score ≥ 5 and ≤ 18 based on the modified NEI grading scheme, with no one region scoring > 3. 5. Anesthetized Schirmer test score ≥ 2 and < 10 mm/5 min in at least 1 eye at the Screening visit. 6. A score of ≥ 35 based on Eye Dryness Score on a Visual Analog Scale (EDS-VAS) at both the Screening and Baseline visits. 7. Investigational product compliance of ≥ 70% and ≤ 130% during the run-in period. 8. Corrected visual acuity equal to or better than logMar +0.7 (Snellen equivalent equal to or better than 20/100), as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at both the Screening and Baseline visits. 9. Good general and ocular health, as determined by the investigator using medical history and ophthalmic examination . 10. 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. 11. Written informed consent from the subject has been obtained prior to any study related procedures. 12. Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits.

Exclusion Criteria:	Subjects meeting any of the following criteria at the Screening visit will be excluded from entry into the study: Ophthalmic: 1. History or presence of any ocular disorder or condition (other than DED) in either eye that would, in the opinion of the investigator, interfere with the interpretation of the study results or subject safety, such as: significant corneal or conjunctival scarring; pterygium or nodular pinguecula; conjunctivitis, or inflammation not associated with DED; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; evidence of keratoconus; etc. Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed. 2. 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. 3. History of ocular surgery within 1 year prior to the Screening 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. History of corneal transplant in one or both eyes. 5. 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. 6. Use of contact lenses in either eye within 7 days prior to the Screening visit or planned use during the study. 7. Punctal or intracanalicular plug present in either eyelid within 14 days prior to the Screening visit or anticipated plug insertion or occlusion at any time during the study. 8. Regular use, as assessed by the investigator, of lid hygiene or heat masks within 14 days prior to the Screening visit or any planned use during the study. 9. Use of lid heating therapy (i.e., LipiFlow®, iLUX®, TearCare®) or Meibomian gland probing/therapeutic expression within 1 year prior to the Screening visit or anticipated during the study. 10. Use of Intense Pulsed Light (IPL) therapy on eyelids within 3 months prior to the Screening visit or anticipated during the study.

	11. Use of artificial tears within 2 hours prior to the Screening visit or anticipated use during the study. 12. Use of any topical ocular anti-inflammatory medication (e.g., ocular cyclosporine [Restasis®, Cequa™, Vevye™, generics], lifitegrast [Xiidra®]) any other prescription ophthalmic product (e.g., perfluorohexyloctane [Meibo™]), for DED, any topical ocular corticosteroid, or any non-steroidal-anti-inflammatory agents within 30 days prior to the Screening visit or anticipated use during the study. 13. Use of topical ocular autologous serum within 30 days prior to the Screening visit or anticipated use during the study. 14. Use of any topical ocular glaucoma medication within 30 days prior to the Screening visit or anticipated use during the study. 15. Regular use, as defined by the investigator, of any other topical ocular medication not listed in Exclusion 11, 12, 13 or 14 within 14 days prior to the Screening visit or anticipated use during the study (e.g., eye whitening products [Visine®, Lumify®], topical ocular antibiotics, topical ocular antihistamines, mast cell stabilizers, age- related blurry near vision (presbyopia) drops [e.g., Vuity™], or other over-the- counter [OTC], herbal, prescription, or nutritional supplements). Note: Occasional short-term use of these topical ocular medications will be permitted provided that no drops were used within 24 hours of the Screening visit or Baseline visits and anticipated use is not within 24 hours of any remaining study visit. 16. Use of Tyrvaya™ (varenicline solution, nasal spray 0.03 mg) within 30 days prior to the Screening visit or anticipated use during the study. 17. 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 prior to the Screening visit or anticipated use during the study. <u>General/Systemic:</u> 18. Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) less than 14 days prior to the Screening visit or a change in dosage is anticipated during the study. <u>Note:</u> Occasional short-term use of medications such as systemic antihistamines will be permitted, provided that use was not within 24 hours of the

	Screening visit or anticipated use within 24 hours of any study visit. 19. Initiation, discontinuation, or change in dose of a systemic corticosteroid less than 60 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Non-ocular topically applied corticosteroids (including topical creams, nasal sprays and inhalers) will be permitted during the study and the dose is not required to be stable 20. Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) less than 60 days prior to the Screening visit or a change in dosage is anticipated during the study. 21. Have received any vaccine within 3 days prior to the Screening or Baseline visit. 22. Use of an investigational product or device within 30 days prior to the Screening visit. 23. At the Screening visit, at the investigator's discretion, have uncontrolled or severe: a. Systemic allergy b. Rhinitis or sinusitis 24. 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.). 25. Known allergies or sensitivity to the study interventions or study diagnostic agents including sodium fluorescein, lissamine green, etc. 26. Positive pregnancy test at Screening or Baseline visits or currently breastfeeding or plans to become pregnant or breastfeed during the study. 27. Women of childbearing potential who are not using a medically acceptable form of birth control. 

	29. 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:	• AR-15512 ophthalmic solution 0.003% • REFRESH® Classic
Evaluation Criteria:	
Efficacy Measures and Endpoints:	Primary Endpoint: • Percentage change from baseline in goblet cell density at Day 90. [redacted]
Safety Measures:	• 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 study medication.
- Full Analysis Set (FAS): The FAS population will include all subjects who have received at least one dose of study medication and have baseline and Day 90 goblet cell density measurements.
- Per-protocol Set (PPS): Includes in the full analysis set having no major protocol deviation that influences efficacy.

Statistical Analyses:

The primary analysis will focus on the percentage change from baseline in goblet cell density analyzed at Day 90. We will use the FAS and PPS as the analysis of covariance model, with treatment and baseline as a covariate. For each treatment group, we will calculate least squares means, standard error, and 90% confidence intervals (CI). The difference between the treatment groups will be tested for statistical significance, evaluated at the 5% (one-sided) level.

[redacted]

Statistical Hypotheses:

Percentage change from baseline in goblet cell density will be tested according to the following: H_0: μ1 = μ2 vs. H_1: μ1 > μ2, where μ_1 = Mean percent change from baseline in goblet cell density for AR-15512 Ophthalmic Solution 0.003% and μ_2 = Mean percent change from baseline in goblet cell density for REFRESH® Classic (Control).

Safety Analysis:

Adverse events will be coded using the latest version of MedDRA. Treatment-emergent adverse events (TEAE) will be summarized using the system organ class (SOC) and preferred terms (PT) based on the safety analysis set.

Corrected visual acuity using LogMAR will be summarized between groups as continuous measures. Slit lamp biomicroscopy will be summarized between groups by frequency and proportion.

Interim Analyses:

No interim analysis will be performed in this study.

Sample Size Determination:

A total sample size of 70 subjects will be randomized in a 1:1 ratio. This sample size will provide at least 90% power to demonstrate the superiority of AR-15512 over REFRESH® Classic in terms of percent change in goblet cell density at the 5% (one-sided) significance level. We assume that the true effect is at least 200% in favor of AR-15512, and standard deviations do not exceed 350% and 75% for AR-15512 and REFRESH®, respectively. These assumptions are based on a published article on the effect of Cyclosporine on globlet cell density in dry eye subjects.

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.

[redacted]

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[redacted]

3 LIST OF ABBREVIATIONS

AE	Adverse Event
BID	Twice Daily
CFR	Code of Federal Regulations
DED	Dry Eye Disease
DHHS	Department of Health and Human Services
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDS-VAS	Eye Dryness Score on a Visual Analog Scale
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IPL	Intense Pulsed Light
IRB	Institutional Review Board
LogMAR	Logarithmic Minimum Angle of Resolution
N/A	Not Applicable
NCS	Not Clinically Significant
NEI	National Eye Institute
ODS-VAS	Ocular Discomfort Score-Visual Analog Scale
SAE	Serious Adverse Event
SANDE	Symptom Assessment in Dry Eye
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent adverse events
TRP	Transient Receptor Potential
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 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 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

The objective of this study is to evaluate the effect of 0.003% AR-15512 to improve the ocular surface characteristics of subjects with DED.

6 CLINICAL HYPOTHESES

The primary clinical hypothesis for this study is that administration of 0.003% AR-15512 leads to an increase in goblet cell density in subjects with DED.

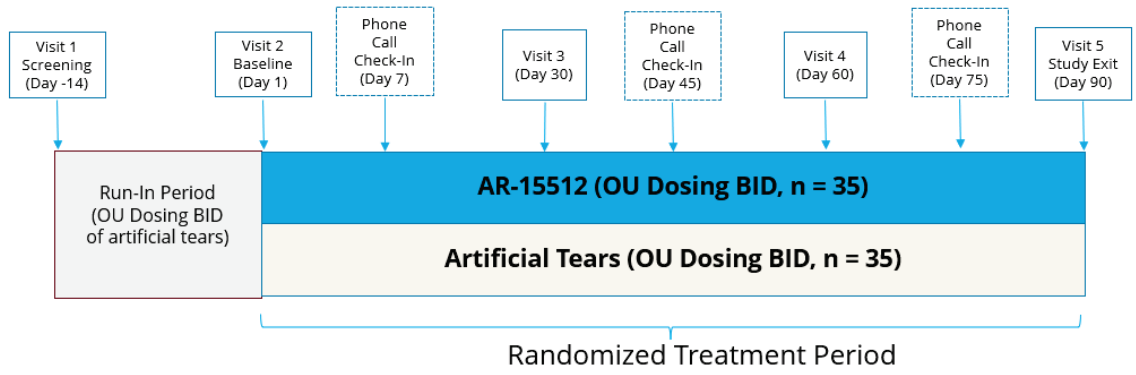
7 OVERALL STUDY DESIGN

This is a Phase 3b, multi-center, comparator-controlled, double-masked, randomized, parallel group study conducted at approximately 4 sites in the United States. All subjects enrolled will have DED. The study will consist of Screening (Day -14) and Baseline (Day 1) visits as well as follow-up visits on Days 30, 60 and 90 (Study Exit). Telephone calls to confirm study treatment dosing compliance will be conducted on Day 7, 45 and 75.

At the end of the Screening visit, all qualified subjects will be assigned to administer Artificial Tears (REFRESH® Classic), twice daily (BID) as one drop in both eyes (OU) for approximately 14 days during the run-in period. After the run-in period, subjects will be re-evaluated at the Baseline visit for signs and symptoms of DED. Only subjects who requalify, based on inclusion/exclusion criteria, will be enrolled in the study and randomized in a 1:1 ratio within each site to receive 0.003% AR-15512 or Artificial Tears (REFRESH® Classic), to be administered as 1 drop BID OU for 90 days.

Impression cytology of the study eye will be performed at Baseline (Day 1) and on Day 90, and impression cytology of the non-study eye will be performed on Day 30. Safety assessments will be conducted at each study visit. An overview of the study design can be found in Figure 1 and details of assessments performed at each visit can be found in the Schedule of Visits and Procedures (Appendix 1).

Figure 1 Study Design Diagram



8 STUDY POPULATION

8.1 Number of Subjects (approximate)

This study is anticipated to enroll approximately 70 subjects with DED, so that approximately 60 subjects complete Day 90 with anticipated dropout rate of 15%. To achieve this goal, approximately 175 subjects may be screened.

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 this trial, an individual must meet all the following criteria:

1. Male or female, 18 years of age or older at the Screening visit.
2. Have a previous history of DED, clinician diagnosed or patient reported, within the previous 6 months prior to the Screening visit.
3. Have used artificial tears for DED symptoms within 2 months prior to the Screening visit.
4. Both of the following signs in the same eye at both the Screening and Baseline visits and the same eye must qualify at both visits:
    a. Total ocular staining score ≥ 10 and ≤ 33 based on the modified National Eye Institute (NEI) grading scheme, with no one region scoring > 3.
    b. Total lissamine green staining score ≥ 5 and ≤ 18 based on the modified NEI grading scheme, with no one region scoring > 3.
5. Anesthetized Schirmer test score ≥ 2 and < 10 mm/5 min in at least 1 eye at the Screening visit.
6. A score of ≥ 35 based on Eye Dryness Score on a Visual Analog Scale (EDS-VAS) at both the Screening and Baseline visits.
7. Investigational product compliance of ≥ 70% and ≤ 130% during the run-in period.
8. Corrected visual acuity equal to or better than logMar +0.7 (Snellen equivalent equal to or better than 20/100), as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at both the Screening and Baseline visits.
9. Good general and ocular health, as determined by the investigator using medical history, ophthalmic examination and history.

10. 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.

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

12. Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits.

8.4 Exclusion Criteria

Subjects meeting any of the following criteria at the Screening and Baseline (Day 1) visits will be excluded from entry into the study:

Ophthalmic:

1. History or presence of any ocular disorder or condition (other than DED) in either eye that would, in the opinion of the investigator, interfere with the interpretation of the study results or subject safety, such as: significant corneal or conjunctival scarring; pterygium or nodular pinguecula; conjunctivitis, or inflammation not associated with DED; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; evidence of keratoconus; etc.
   Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed.

2. 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.

3. History of ocular surgery within 1 year prior to the Screening 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. History of corneal transplant in one or both eyes.

5. 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.

6. Use of contact lenses in either eye within 7 days prior to the Screening visit or planned use during the study.

7. Punctal or intracanalicular plug present in either eyelid within 14 days prior to the Screening visit or anticipated plug insertion or occlusion at any time during the study.

8. Regular use, as assessed by the investigator, of lid hygiene or heat masks within 14 days prior to the Screening visit or any planned use during the study.

9. Use of lid heating therapy (i.e., LipiFlow®, iLUX®, TearCare®) or Meibomian gland probing/therapeutic expression within 1 year prior to the Screening visit or anticipated during the study.

10. Use of Intense Pulsed Light (IPL) therapy on eyelids within 3 months prior to the Screening visit or anticipated during the study.

11. Use of artificial tears within 2 hours prior to the Screening visit or anticipated use during the study.

12. Use of any topical ocular anti-inflammatory medication (e.g., ocular cyclosporine [Restasis®, Cequa™, Vevye™, generics], lifitegrast [Xiidra®]) any other prescription ophthalmic product (e.g., perfluorohexyloctane [Meibo™]) for DED, any topical ocular corticosteroid, or any non-steroidal-anti-inflammatory agents within 30 days prior to the Screening visit or anticipated use during the study.

13. Use of topical ocular autologous serum within 30 days prior to the Screening visit or anticipated use during the study.

14. Use of any topical ocular glaucoma medication within 30 days prior to the Screening visit or anticipated use during the study.

15. Regular use, as defined by the investigator, of any other topical ocular medication not listed in Exclusion 11, 12, 13 or 14 within 14 days prior to the Screening visit or anticipated use during the study (e.g., eye whitening products [Visine®, Lumify®], topical ocular antibiotics, topical ocular antihistamines, mast cell

stabilizers, age- related blurry near vision (presbyopia) drops [e.g., Vuity™], or other over-the- counter [OTC], herbal, prescription, or nutritional supplements). Note: Occasional short-term use of these topical ocular medications will be permitted provided that no drops were used within 24 hours of the Screening visit or Baseline visits and anticipated use is not within 24 hours of any remaining study visit.

16. Use of Tyrvaya™ (varenicline solution, nasal spray 0.03 mg) within 30 days prior to the Screening visit or anticipated use during the study.

17. 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 prior to the Screening visit or anticipated use during the study.

General/Systemic:

18. Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) less than 14 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Occasional short-term use of medications such as systemic antihistamines will be permitted, provided that use was not within 24 hours of the Screening visit or anticipated use within 24 hours of any study visit.

19. Initiation, discontinuation, or change in dose of a systemic corticosteroid less than 60 days prior to the Screening visit or a change in dosage is anticipated during the study.
    Note: Non-ocular topically applied corticosteroids (including topical creams, nasal sprays and inhalers) will be permitted during the study and the dose is not required to be stable

20. Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) less than 60 days prior to the Screening visit or a change in dosage is anticipated during the study.

21. Have received any vaccine within 3 days prior to the Screening or Baseline visit.

22. Use of an investigational product or device within 30 days prior to the Screening visit.

23. At the Screening visit, at the investigator's discretion, have uncontrolled or severe:

    c. Systemic allergy

    d. Rhinitis or sinusitis

24. 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.).

25. Known allergies or sensitivity to the study interventions or study diagnostic agents including sodium fluorescein, lissamine green, etc.

26. Positive pregnancy test at Screening or Baseline visits or currently breastfeeding or plans to become pregnant or breastfeed during the study.

27. Women of childbearing potential who are not using a medically acceptable form of birth control.

29. 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.

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).

8.6 Study Eye Selection Criteria

Study eye is defined as the eye with greatest lissamine green staining at Baseline. If both eyes have the same level of LG staining, then, study eye will be the one that has the greatest total ocular staining. In the event both eyes record the same level of staining, right eye will be chosen as the study eye.

9 STUDY PARAMETERS

9.1 Efficacy Measures and Endpoints

9.1.1 Primary Efficacy Measure(s)

The following primary efficacy endpoint will be evaluated:

- Percentage change from baseline in goblet cell density at Day 90.

9.2 Safety Measures

- Corrected Visual Acuity
- Slit-lamp biomicroscopy

- Adverse Events (AE)

10 STUDY MATERIALS

10.1 Study Treatment(s)

10.1.1 Study Treatment/Formulation

Run-in Period:

- Artificial Tears (REFRESH® Classic)

Randomized Treatment:

Subjects will be assigned to one of two possible dose arms in a 1:1 ratio at the Baseline visit:

- AR-15512 ophthalmic solution 0.003%
- Artificial Tears (REFRESH® Classic)

10.1.2 Instructions for Use and Administration

Run-in:

Subjects who qualify at the Screening visit will self-administer their first dose of run-in intervention under site staff supervision. Subjects will be instructed on proper administration procedures as follows: 1 drop in each eye in the morning (from approximately 7:00h to 10:00h) and 1 drop in each eye in the evening (from approximately 19:00h to 22:00h). A new vial should be used for each administration time (both eyes dosed from one vial).

Randomized Treatment:

Following the run-in period, those subjects who requalify at the Baseline visit, will be re-instructed on proper administration procedures at the Baseline visit and the first dose of randomized treatment will be self-administered under site-staff supervision. Subjects will be instructed to administer their randomized study intervention as follows: 1 drop in each eye in the morning (from approximately 7:00h to 10:00h) and 1 drop in each eye in the evening (from approximately 19:00h to 22:00h). A new vial should be used for each administration time (both eyes dosed from one vial). The “morning” dose of randomized

study intervention should **not be taken** prior to each follow up clinic visit (Days 30, 60 and 90).

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 Section 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

Prior the initiation of study run-in at Visit 1, each subject who provides written informed consent 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. Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1 and Visit 2 will be assigned a randomization number at the end of Visit 2.

The Interactive Web Response System (IWRS) will be used to assign all randomization numbers. Randomization and kit numbers will be assigned automatically to each subject as they are entered into the IWRS.

An independent (unmasked) person at the site who is not responsible for performing any of the study procedures is to be assigned to dispense, collect, and store study drug while maintaining the masking of the study.

The independent site staff will dispense kit(s) required until the next visit. Both the randomization number and the dispensed study drug kit number(s) will be recorded on the subject's source document and electronic case report form (eCRF). Subjects, Sponsor, Contract Research Organization (CRO), and all other site personnel will be masked to treatment assignmentDemographics

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

11.2 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 Screening visit, must also be recorded. All relevant medical and ophthalmic surgical procedures must be recorded.

11.3 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 Screening Visit or receives during the study must be recorded. Prior medications taken up to at least 30 days prior to the Screening Visit must also be recorded.

11.3.1 Prohibited Medications/Treatments

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

11.3.2 Escape Medications

No escape medications are required for this study.

11.3.3 Special Diet or Activities

No special diets or activities are required for this study.

11.4 Clinical Laboratory Tests

11.4.1 Pregnancy Testing

Urine pregnancy tests for women of childbearing are required at the Screening and Baseline visits as well as the Exit (Day 90). 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.

11.5 Dispensing Study Intervention

Masked study-related site personnel will be cautioned that any used or unused study intervention kits are not to be opened at the clinical site by the site staff involved in efficacy or safety assessments.

Unmasked study staff responsible for dispensing study intervention will be listed on the Site Authorization and Delegation Log. When a subject meets all criteria for enrollment, the subject will be randomly assigned to a study intervention according to the IWRS. The responsible unmasked study staff will account for all used and unused study kits / vials by maintaining a Study Intervention Accountability log.

Masked trial personnel must avoid seeking information that may compromise masking. Unmasked trial personnel must not disseminate information that is potentially unmasking to any masked personnel. The masked and unmasked site personnel must coordinate all trial activities as necessary to protect masking and minimize bias during the trial.

The investigational product will be provided in masked identical kits. Study intervention kits will be distributed at the end of the Screening, Baseline (Day 1), Day 30 and Day 60 visits.

11.6 Efficacy Assessment

11.6.1 Impression Cytology

Impression cytology samples will be collected from **study eye** on Day 1 (Baseline) and Day 90.

[redacted]

11.7 Safety Assessments

11.7.1 Corrected Visual Acuity

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.

11.7.2 Biomicroscopy

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant ((CS); 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.

11.8 Other Assessments

- Anesthetized Schirmer test
- Eye dryness questionnaire (Visual Analog Scale [VAS])
- Sodium Fluorescein Staining of the Cornea Based on the Modified National Eye Institute (NEI) Grading Scheme
- Lissamine Green Staining of the Conjunctiva Based on the Modified National Eye Institute Grading Scheme

Additional details are found in the Manual of Procedures.

11.9 Examination Procedures

11.9.1 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.

11.10 Schedule of Visits, Measurements, and Dosing

11.10.1 Scheduled Visits

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

11.10.2 Unscheduled Visits

These visits may be performed per instructions provided in the MOP 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."

11.11 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of artificial tears at the end of Visit 1, and proper instillation and storage of study drug at the end of Visit 2 through 4 and given written instructions. Study drug accountability will be performed throughout the trial. Dosing compliance will be based on the used and unused vials count. If the subject is less than 70% or more than 130% compliant with dosing based on the expected number of used vials, then the subject will be deemed non-compliant, and a deviation should be recorded.

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.

11.12 Subject Disposition

11.12.1 Completed Subjects

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

11.12.2 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.

11.12.3 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.

11.13 Study Termination

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

If the clinical study is prematurely terminated or suspended:

- The study sponsor or Ora must:
    - Immediately notify the investigator(s) and subsequently provide instructions for study termination.
    - Inform the investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.
- The investigator must:

- Promptly notify the IRB of the termination or suspension and of the reasons.
- Provide subjects with recommendations for post-study treatment options as needed.

11.14 Study Duration

An individual subject's participation will involve 8 visits (5 on-site and 3 via telephone) over approximately 15 weeks.

11.15 Monitoring and Quality Assurance

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

11.16 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.

- **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.

- 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 or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure 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 a serious or non-serious AE or adverse reaction is unresolved at the time of exit, efforts will be made to follow up until the AE or adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event. These follow-up visits will be documented.

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 treatment emergent adverse events (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.

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 Investigator's Brochure 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 Investigator's Brochure 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 Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or ARs 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.

- 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 Investigator's Brochure.

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

12.4.1 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 Investigator's Brochure. 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, IRB, and Investigators at each of the study sites will be informed as required.

12.4.2 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, observation, 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.

12.4.3 SAE Report Contact Information

12.5 Procedures for Unmasking

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

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

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact Ora and/or the medical monitor prior to unmasking the identity of the IP, if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify the Sponsor, and jointly will determine if the unmasking request should be granted. They may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject using IWRS. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the Trial Master File (TMF). For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject must be noted in the subject's study file.

Unmasked subjects will be discontinued from the study. Unmasked subjects will be followed for safety monitoring until resolution of the adverse event or study completion, whichever occurs last.

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

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-ups 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 sent to IQVIA within 24 hours of the site's awareness of the new information (See Section 12.4.3 for contact 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.

12.7 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 nondevice constituents of the study intervention. Nondevice 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 study medication.
- Full Analysis Set (FAS): The FAS population will include all subjects who have received at least one dose of study medication and have baseline and Day 90 goblet cell density measurements.
- Per-protocol Set (PPS): Includes in the full analysis set having no major protocol deviation that influences efficacy.

13.2 Statistical Hypotheses and Analyses Supporting Key Study Objectives

The primary hypothesis will focus on the percent change from baseline in goblet cell density on the FAS and PPS. This measurement is calculated as follows:

$$\text{Percent (\%) Change} = 100 \times \frac{\text{Goblet Cell Density at Day 90} - \text{Baseline Goblet Cell Density}}{\text{Baseline Goblet Cell Density}}$$

The primary efficacy hypothesis are as follows:

H_0: $\mu 1 = \mu 2$ vs.

H_1: $\mu 1 > \mu 2$,

Where $\mu 1$ = Mean percent change from for AR-15512 Ophthalmic Solution 0.003% and $\mu 2$ = Mean percent change from for the control group, REFRESH® Classic.

To analyze this, we will use an analysis of covariance (ANCOVA) model. This model includes treatment and baseline goblet cell density as a covariate. We will calculate, least squares means, standard error and 90% confidence intervals (CI) for each treatment group. The difference between the groups will be tested for statistical significance, which will be evaluated at the 5% (one-sided) level. Descriptive statistics such as the mean, standard deviation, minimum and maximum will be generated.

Analysis of endpoints based on proportions will be conducted using Chi-square test. Study success will be determined based on the primary endpoint. Other endpoints will not be included in the testing strategy and will be considered supportive.

13.3 Safety Analysis

Adverse events will be coded using the latest version of MedDRA. Treatment-emergent adverse events (TEAE) will be summarized using the system organ class (SOC) and preferred terms (PT) based on the safety analysis set. Related TEAE and TEAE by maximum grade will be summarized. No inferential statistics will be reported for adverse events.

Corrected visual acuity using LogMAR will be summarized between groups as continuous measures. When data permit, an ANCOVA will be used for logMAR. Slit lamp biomicroscopy will be summarized between groups by frequency and proportion at each timepoint.

13.4 Sample Size Determination

A total sample size of 70 subjects will be randomized in a 1:1 ratio. This sample size will provide at least 90% power to demonstrate the superiority of AR-15512 over REFRESH® Classic in terms of percent change in goblet cell density at the 5% (one-sided) significance level. We assume that the true effect is at least 200% in favor of AR-15512, and standard deviations do not exceed 350% and 75% for AR-15512 and REFRESH®, respectively. These assumptions are based on a published article on the effect of Cyclosporine on globlet cell density in dry eye subjects.

No data currently exists characterizing the ability of 0.003% AR-15512 to increase goblet cell density. Leveraging the literature, while plentiful, is difficult due to several important variables including method of sample collection (impression cytology vs biopsy), conjunctival sampling location (goblet cell density is known to be distributed differently around the conjunctiva), the counting methodologies and scales used, and the actual expression of data (absolute numbers vs percentage change vs categorical scales). However, there is precedent in the literature to support two key points: (1) a correlation exists between improvements in conjunctival staining and increases in goblet cell density and (2) sample size of 10 – 30 subjects per arm provide adequate power to detect treatment differences of at least a 100% change.

13.5 Interim Analyses

No interim analyses will be performed in this study.

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/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 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 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 Study Intervention

14.5.1 Labeling/Packaging

The study interventions will be packaged and labeled into clinical kits. All clinical kits will be labeled according to applicable regulatory requirements.

14.5.2 Storage of Study Intervention

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

AR-15512 0.003% ophthalmic solution should be stored refrigerated at a controlled temperature (2 to 8°C/36 to 46°F) until dispensed to the subject.

At time of dispensing, the subject will be instructed to store the study treatment at room temperature (store in carton) as directed on the investigational label. Subjects should be instructed not to refrigerate or freeze the study treatment. See more details in the Pharmacy Manual.

Note: The artificial tears will be stored in accordance with the manufacturer's instructions.

14.5.3 Accountability of Investigational Product

The study intervention 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 study intervention must only be distributed to subjects properly qualified under this protocol to receive the study intervention.

The investigator must keep an accurate accounting of the study intervention received from the supplier. This includes the amount of study intervention dispensed to subjects, the amount of study intervention 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 study intervention.

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. Subjects should be instructed to retain all vials (used, partially used or unused) of study intervention and return them to the clinical site. 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

Craig, J. P., K. K. Nichols, E. K. Akpek, B. Caffery, H. S. Dua, C. K. Joo, Z. Liu, J. D. Nelson, J. J. Nichols, K. Tsubota and F. Stapleton (2017). "TFOS DEWS II Definition and Classification Report." Ocul Surf **15**(3): 276-283.

16 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

	Start of 2 Week Run-In (Refresh Complete)	Intervention Period (BID OU, 1:1 0.003% AR-15512: Refresh Complete)							
Visit	**Visit 1 Screening**	**Visit 2 Baseline**	**Phone Call**	**Visit 3**	**Phone Call**	**Visit 4**	**Phone Call**	**Visit 5 Study Exit**	**Early Termination**
Visit Window (Days)	**Day -14 (+3[2])**	**Day 1**	**Day 7 (±3)**	**Day 30 (±3)**	**Day 45 (±3)**	**Day 60 (±3)**	**Day 75 (±3)**	**Day 90 (±3)**	
Informed consent	X								
Inclusion and exclusion criteria	X	X							
Demographics	X								
Collection of unused study treatment		X		X		X		X	X
Medical, ophthalmic, and surgical history	X								
Prior or concomitant medication review	X	X		X		X		X	X
Adverse events review	X	X	X	X	X	X	X	X	X
Urine pregnancy test (WOCBP only)	X	X						X	X
Eye dryness (EDS-VAS) questionnaire	X	X							
Corrected visual acuity	X	X		X		X		X	X
Slit-lamp biomicroscopy	X	X		X		X		X	X

	Start of 2 Week Run-In (Refresh Complete)	Intervention Period (BID OU, 1:1 0.003% AR-15512: Refresh Complete)							
Visit	**Visit 1 Screening**	**Visit 2 Baseline**	**Phone Call**	**Visit 3**	**Phone Call**	**Visit 4**	**Phone Call**	**Visit 5 Study Exit**	**Early Termination**
Visit Window (Days)	**Day -14 (+3[2])**	**Day 1**	**Day 7 (±3)**	**Day 30 (±3)**	**Day 45 (±3)**	**Day 60 (±3)**	**Day 75 (±3)**	**Day 90 (±3)**	
Fluorescein staining of cornea (modified NEI grading scale)	X	X							
Lissamine green staining of conjunctiva (modified NEI grading scale)	X	X							
At least 10 minute rest period	X								
At least a 60 minute rest period		X							
Anesthetized Schirmer test	X								
Review of qualification	X	X							
Randomization		X							
Dispensing of study treatment	X	X		X		X			
Compliance Check			X		X		X		
Impression cytology of **study eye only with EyePrim**		X						X	
In office administration of study treatment to both eyes 15-20 mins after Impression cytology on Day 1		X							
In Office administration of study treatment to both eyes on Day 30				X					

	Start of 2 Week Run-In (Refresh Complete)	Intervention Period (BID OU, 1:1 0.003% AR-15512: Refresh Complete)							
Visit	**Visit 1 Screening**	**Visit 2 Baseline**	**Phone Call**	**Visit 3**	**Phone Call**	**Visit 4**	**Phone Call**	**Visit 5 Study Exit**	**Early Termination**
Visit Window (Days)	**Day -14 (+3[2])**	**Day 1**	**Day 7 (±3)**	**Day 30 (±3)**	**Day 45 (±3)**	**Day 60 (±3)**	**Day 75 (±3)**	**Day 90 (±3)**	
only[1]									
3 minutes after administration of study treatment administer anesthetic to BOTH eyes (Day 30 day only)[1]				X					
[redacted]									
In office administration of study treatment to both eyes on Day 60						X			
Corrected visual acuity post impression cytology		X		X				X	
Slit-lamp biomicroscopy post impression cytology		X		X				X	
Study exit								X	X

Abbreviations: EDS-VAS = Eye Dryness Score on a Visual Analog Scale ; NEI = National Eye Institute; WOCBP = women of childbearing potential

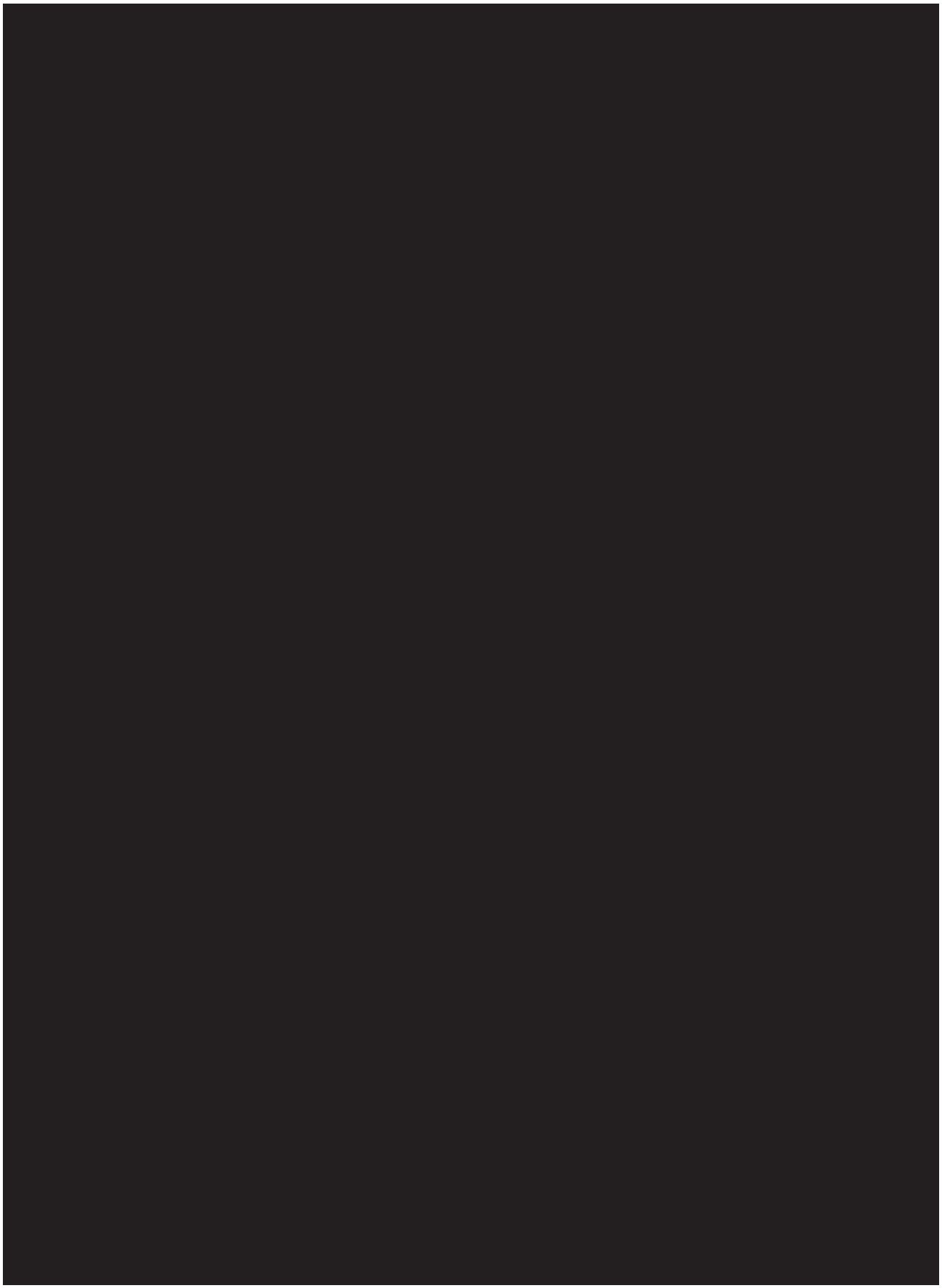
[1] Impression cytology of the non-study eye on Day 30 can be cancelled at the Investigator's discretion, if, in their opinion, impression cytology may negatively impact tolerability of the study medication.

Note: Subjects should be instructed to NOT take their study treatment the morning of the Clinic Visit as will be dosed in clinic (Days 30 and 60) or exited (Day 90).

[2] The Baseline Visit should be scheduled between 11 and 14 days after the Screening Visit.

APPENDIX 2 HANDLING OF BIOLOGICAL SPECIMENS

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



APPENDIX 5: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Phase 3b Study to Investigate the Effect of 0.003% AR-15512 on the Ocular Surface Characteristics of Subjects with Dry Eye Disease
Protocol Number:	DEF512-E003
Final Date:	21 Aug 2024

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.

Signed:_____ Date:_____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____