A Long-Term Safety Study Evaluating the Safety and Systemic Exposure of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease (COMET-4)

STUDY ID:

AR-15512-LTSS

PROTOCOL

NCT05493111

Clinical Study Protocol

Study Title:	A Long-Term Safety Study Evaluating the Safety and Systemic Exposure of AR-15512, a **C**o**l**d Ther**m**o**r**eceptor Modula**t**or, for the Treatment of Dry Eye Disease (COMET-4)
Study Number:	AR-15512-LTSS
Study Phase:	3
Product Name:	AR-15512
Indication:	Dry Eye Disease
Investigators:	Multicenter

Sponsor:	Aerie Pharmaceuticals, Inc.
Sponsor	4301 Emperor Boulevard Suite 400
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[redacted]

NCT Number: 05493111

	Date
Original Protocol (Rev 0):	22 August 2022

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CLINICAL PROTOCOL CONTACT INFORMATION

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Long-Term Safety Study Evaluating the Safety and Systemic Exposure of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease (COMET-4)

Study No: AR-15512-LTSS

Original Protocol Date: 22 August 2022

Protocol Version No: Original Protocol

Protocol Version Date: 22 August 2022

Role	Contact information
[redacted]	

SYNOPSIS

Sponsor:
Aerie Pharmaceuticals, Inc.

Name of Finished Product:
AR-15512 ophthalmic solution 0.003%

Name of Active Ingredients:
AR-15512

Study Title:
A Long-Term Safety Study Evaluating the Safety and Systemic Exposure of AR-15512, a **C**o**l**d Ther**m**o**r**eceptor Modula**t**or, for the Treatment of Dry Eye Disease (COMET-4)

Study Number:
AR-15512-LTSS

Study Phase:
3

Primary Objective:
To evaluate the safety of topical ophthalmic 0.003% AR-15512 compared to its vehicle dosed twice daily (BID) in subjects with dry eye disease (DED) for 12 months

Study Design:
This will be a 12 month, multicenter, vehicle-controlled, double-masked, randomized study conducted at approximately 10 sites in the United States. All subjects enrolled will have DED. The study will consist of a Baseline (Day 1) visit as well as visits on Day 14, Day 90, Day 180, Day 270, and Day 365 (Study Exit). In addition, there will be dispensing visits on Days 45, 135, 225, and 315.

Subjects who qualify at the Baseline visit, based on inclusion/exclusion criteria, will be enrolled in the study and randomized in a 2:1 ratio within each site, to receive either 0.003% AR-15512 or AR-15512 vehicle to be administered BID as 1 drop in each eye for 12 months. Systemic pharmacokinetic (PK) evaluation will be performed in a subset of subjects (n=35).

Study Population:
This study is anticipated to randomize approximately 270 subjects with DED. Approximately 108 subjects out of 180 subjects randomized to receive 0.003% AR-15512 and 54 subjects out of 90 subjects randomized to receive vehicle are expected to reach the Day 365 visit. The anticipated dropout rate is 40%. To achieve this goal, approximately 360 subjects may be screened.

Key Inclusion Criteria
Subjects must meet all of the following criteria to enter into the study:

- Have a previous history of DED, clinician diagnosed or patient reported, within the previous 12 months of the Baseline visit
- Have used or desired to use artificial tears for DED symptoms within 3 months prior to the Baseline visit

- 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 the Baseline visit

- Good general and ocular health, as determined by the investigator using medical history, ophthalmic examination and history, and vital signs (heart rate and blood pressure) at the Baseline visit

Key Exclusion Criteria

Subjects meeting any of the following criteria at the Baseline visit (i.e., qualification visit) will be excluded from entry into the study:

- History or presence of any severe ocular disorder or condition (other than DED) in either eye that is, in the opinion of the investigator, likely to interfere with subject safety or evaluation, 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.)
- Current evidence of other significant ophthalmic disease requiring topical medication (e.g. glaucoma, ocular hypertension), which may interfere with vision (e.g., cataract, macular degeneration) or other disease which the investigator believes may interfere with study findings or interpretation
- Use of contact lenses in either eye within 7 days prior to the Baseline visit or planned use during the study
- Use of any topical ocular anti-inflammatory medication within 30 days prior to the Baseline visit or anticipated use during the study (e.g., ocular cyclosporine [Restasis®, Cequa™], lifitegrast [Xiidra®], or any other prescription ophthalmic product for DED, topical ocular corticosteroid- or non-steroidal-anti-inflammatory agents
- Use of artificial tears within 2 hours prior to the Baseline visit
- Use of topical ocular autologous serum within 30 days prior to the Baseline visit or anticipated use during the study
- Use of any topical ocular glaucoma medication within 30 days prior to the Baseline visit or anticipated use during the study
- Use of Tyrvara™ (varenicline solution, nasal spray 0.03mg) within 30 days prior to the Baseline visit or anticipated use during the study
- 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 Baseline visit or anticipated use during the study
- Use of lid heating therapy (i.e., LipiFlow®, iLUX®) or Meibomian gland probing/therapeutic expression within 6 months prior to the Baseline visit or anticipated during the study
- Randomization to a study arm in Phase 2b AR-15512-CS201 (COMET-1) study, Phase 3 AR-15512-CS301 (COMET-2) study or Phase 3 AR-15512-CS302 (COMET-3) study.

Study Interventions and Dosing Regimens:

Randomization (2:1)

- Topical ocular administration of one drop of 0.003% AR-15512 ophthalmic solution in both eyes BID
- Topical ocular administration of one drop of AR-15512 vehicle in both eyes BID

Duration of Study:

Approximately 12 months (365 days)

Safety Assessments:

- Adverse events
- Vital signs (heart rate and blood pressure)
- Endothelial cell counts
- Hematology, chemistry, and urinalysis
- Best corrected visual acuity (Baseline and Exit visits only)
- Corrected visual acuity

- Biomicroscopy
- Total ocular staining
- Intraocular pressure (IOP)
- Dilated fundus exam

Pharmacokinetics

- Systemic exposure (plasma pharmacokinetic parameters (selected sites))

[redacted]

Statistical Methods:

Determination of Sample Size

This study is designed to determine the long-term safety of 0.003% AR-15512. Approximately 270 subjects will be randomized in a 2:1 ratio to receive 0.003% AR-15512 (180 subjects) or AR-15512 vehicle (90 subjects). Assuming a dropout rate of 40%, approximately 108 subjects randomized to receive 0.003% and 54 subjects randomized to receive vehicle are expected to reach the Day 365 visit.

With 108 subjects completing 1 year (365 days) on 0.003% AR-15512, the study will have 96% probability to detect adverse events that occur at a true rate of 3% or greater. That is, with 108 subjects completing 1 year (365 days) on the investigational product, if a specific adverse event is not observed, then with 96% confidence, that adverse event occurs at a true rate of <3%.

Analysis methods

Frequencies and percentages of treatment-emergent adverse events (TEAEs) will be summarized for 0.003% AR-15512 and vehicle.

Other safety endpoints including vital signs, endothelial cell counts, laboratory parameters (hematology, chemistry, and urinalysis), corrected visual acuity, best corrected visual acuity, biomicroscopy, total ocular staining, IOP, and dilated fundoscopy will be summarized by treatment group and visit using descriptive statistics. For assessments performed by eye, each eye will be summarized separately.

Plasma pharmacokinetic parameters including AR-15512 area under the plasma concentration time curve (AUC), maximum recorded concentration (C_{max}), minimum recorded concentration (C_{min}), time of maximum concentration (T_{max}) will be summarized. R_{Cmax} and R_{AUC} (where R represents an accumulation factor) will be calculated.

[redacted]

Date of Original Approved Protocol (Rev 0): 22 August 2022

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AR	Adverse Reaction
AUC	Area Under the Curve
BCVA	Best Corrected Visual Acuity
BID	Twice Daily
BPM	Beats Per Minute
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
CS	Clinically Significant
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRAS	Generally Recognized as Safe
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization

IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
LogMAR	Logarithmic Minimum Angle of Resolution
LS	Least Square
NCS	Not Clinically Significant
NDA	New Drug Application
ODS	Ocular Discomfort Score
PK	Pharmacokinetic
R_{AUC}	Accumulation Ratio Based Upon Area Under the Curve
R_{Cmax}	Accumulation Ratio Based Upon Maximum Plasma Concentration
SAE	Serious Adverse Event
[redacted]	
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TID	Three Times a Day
T_{max}	Time of Maximum Concentration
TRPM8	Transient Receptor Potential Melastatin 8
[redacted]	
WOCBP	Women of Child-Bearing Potential

1. INTRODUCTION

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 dry eye disease (DED).

1.1 Background

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). Epidemiological data suggest the prevalence of DED falls in the range of 5% to 50% of the global population ≥ 50 years old, depending on the definition of DED that was used (Baudouin 2014, Bron 2014, Rolando 2010, Smith 2007, Stapleton 2017, Uchino 2013).

DED is broadly attributed to either impaired tear film production or excessive tear film evaporation. Either of these changes to the tear film can compromise the health of the ocular surface with associated epithelial damage, which can adversely affect visual function. This can be experienced as blurred vision and ocular surface discomfort, often described as a feeling of dryness, burning, itchiness, or a sandy/gritty sensation.

Treatment of DED is mainly symptomatic and very few specific pharmacologic therapies are currently approved (Jones 2017). Artificial tear preparations are generally the first therapy considered. Artificial tears are based on lubricating or viscosity-increasing agents and there is limited evidence suggesting that any one type of artificial tear is markedly better than others (Doughty 2009). With respect to pharmaceuticals, various strategies exist for targeting the underlying ocular inflammation associated with DED with two products (Restasis® [0.05% cyclosporine ophthalmic emulsion] and Cequa™ [0.09% cyclosporine ophthalmic solution]) indicated for increased tear production in patients with DED and a third, Xiidra® (5.0% lifitegrast ophthalmic solution), indicated for the treatment of the signs and symptoms of DED. In addition, a novel cholinergic agonist, delivered nasally (varenicline solution, nasal spray 0.03mg [Tyrvaya™]), is approved for the treatment of signs and symptoms of DED. The short-term application of topical ocular steroids is also used for acute management of DED.

In recent years, increased attention has been placed on the neuronal regulation of tear production. The trigeminal nerve provides the pathway for parasympathetic stimulation of the lacrimal functional unit and sensory stimulation of the cornea and conjunctiva is essential for initiating basal tear production (Belmonte 2015; Belmonte 2017). Reduced corneal neuron density and / or dysfunction of the corneal sensory nerves have been hypothesized to contribute to the pathogenesis of DED. The functional types of sensory nerve fibers of the cornea are distinguished by their selective expression of different transient receptor potential channels, each of which confers a specific sensitivity to mechanical, thermal, or chemical stimuli.

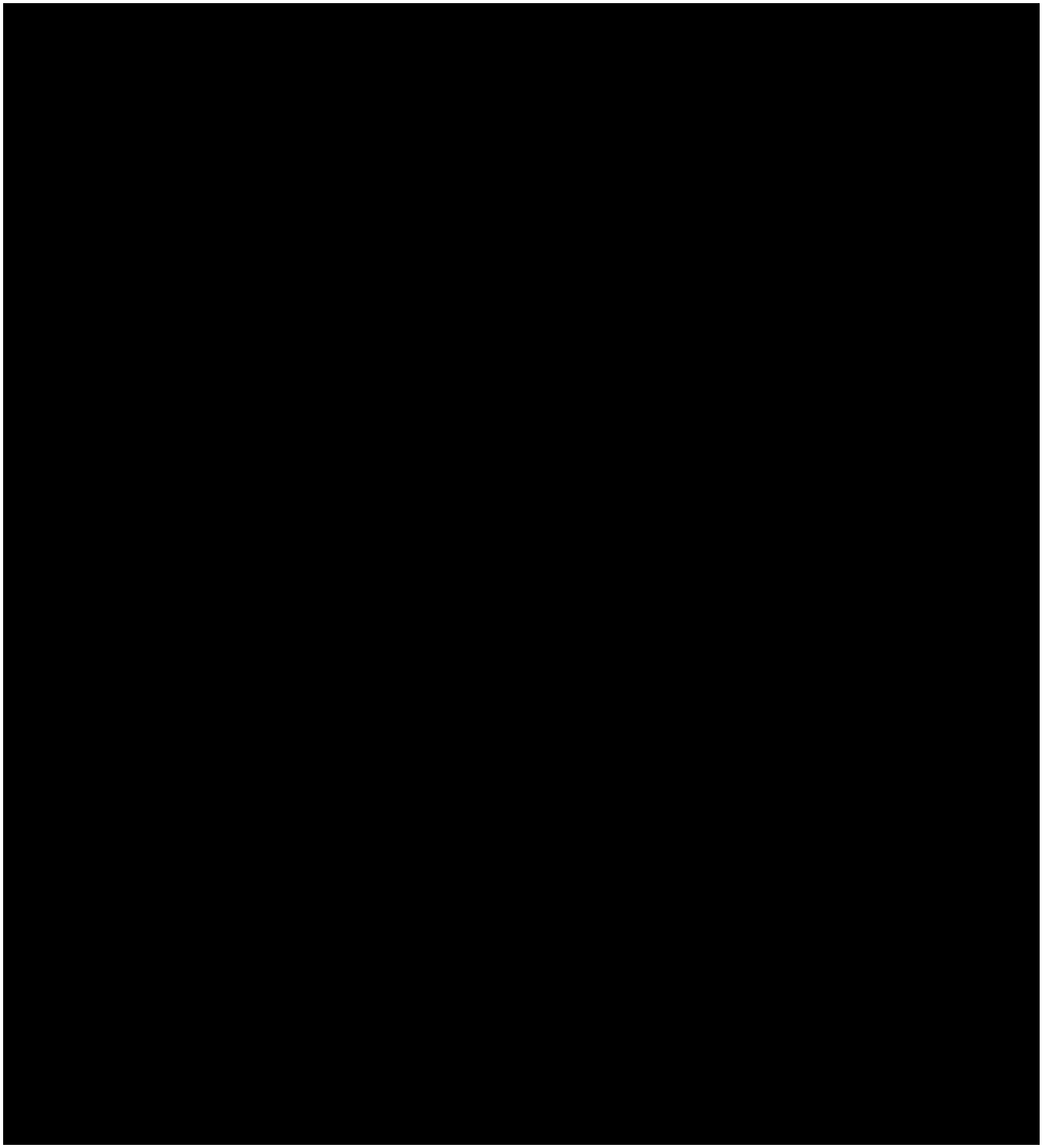
Branches of the trigeminal nerve innervating the cornea and lids selectively express cold sensitive thermoreceptors, called TRPM8 receptors (Belmonte 2017, Viana 2011). TRPM8 receptors are associated with the detection of ocular surface dryness and are activated by evaporative cooling and hyperosmolarity leading to regulation of tear production and blink rate (Belmonte 2017, Yang 2017, Yang 2018). In addition, agonists of TRPM8 promote a cooling sensation that may be beneficial for reducing ocular discomfort and pain. Taken together, TRMP8 agonists may have a dual role in the potential treatment of DED by both stimulation of tear production and reduction of discomfort (Abelson 2013).

AR-15512 is a potent and selective agonist of TRPM8 that has been used as a flavoring agent or adjuvant in the food industry and as cooling agent for chewing gum and candies for several years. AR-15512 was acquired by Aerie in connection with the acquisition of Avizorex Pharma S.L. ("Avizorex"), who began the development of AR-15512 ophthalmic solution.

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 which 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.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AR-15512 is provided in the investigator's brochure (IB). [redacted]

[redacted]



1.3 Risk/Benefit Assessment

AR-15512 has been used as a flavoring agent or adjuvant in the food industry and as a cooling agent for chewing gum and candies for more than a decade. AR-15512 (FL-no. 16.123) is generally recognized as safe (GRAS) as a flavoring agent or adjuvant

(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).

In vitro, *in vivo* and *ex vivo* studies have also been performed on AR-15512 to demonstrate safety, tolerability and negligible systemic exposure and to characterize the effective dose and the regimen of ocular administration of AR-15512 ophthalmic solution. In addition, Aerie has conducted two good laboratory practice (GLP) 3-month repeated-dose topical ocular toxicity studies of AR-15512 ophthalmic solution in rabbits on clinical formulations and higher dose regimens then reflected in this Phase 3 study.

[redacted]

DED represents a significant health care burden, contributing to approximately 25% of visits to ophthalmic clinics (Gayton 2009, Reddy 2004, Yu 2011), and can significantly affect a patient's daily activities and quality of life. Studies have shown that DED interferes with reading, driving ability, computer use, work productivity and is associated with increased anxiety, stress, and depression (Noor 2018).

Currently there are few effective treatments for DED. Artificial tears, which are comprised of various polymers and buffering excipients are formulated to soothe and lubricate the ocular surface and are usually the initial option for all DED patients. Artificial tears are generally palliative in nature and do not halt disease progression. With respect to pharmaceuticals, various strategies exist for targeting the underlying ocular inflammation associated with DED, but only one (5% lifitegrast [Xiidra®]), is indicated for the treatment of the signs and symptoms of DED. In addition, a novel cholinergic agonist, delivered nasally (varenicline solution, nasal spray 0.03mg [Tyrvaya™]), is approved for the treatment of signs and symptoms of DED.

Thus, there is a significant unmet need for an effective topical ocular therapeutic to effectively treat the signs and symptoms of DED. This unmet need in combination with all pre-clinical and clinical data collected to date support continued development of AR-15512 as a potential new treatment for DED with a high overall positive benefit-risk ratio to humans.

2. STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the safety of topical ophthalmic 0.003% AR-15512 compared to its vehicle dosed BID in subjects with DED for 12 months.

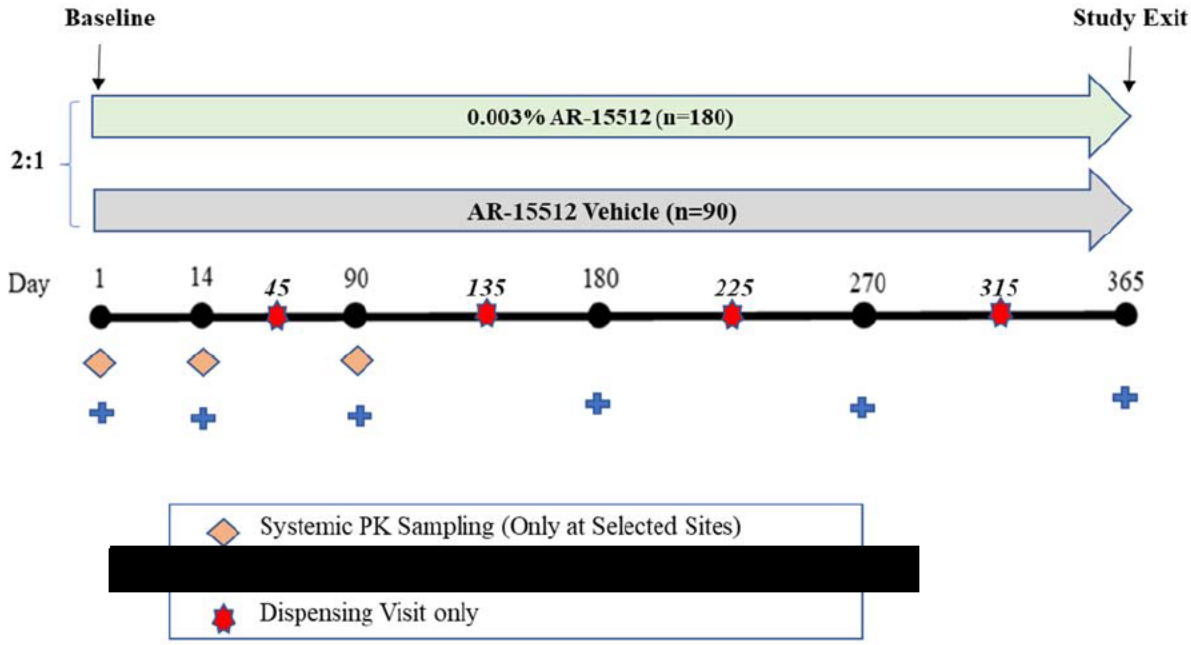
3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This will be a 12 month, multicenter, vehicle-controlled, double-masked, randomized study conducted at approximately 10 sites in the United States. All subjects enrolled will have DED. The study will consist of a Baseline (Day 1) visit as well as follow-up visits on Days 14, 90, 180, 270, and 365 (Study Exit). In addition, there will be dispensing visits on Days 45, 135, 225, and 315. A schematic of the overall study design can be found in Figure 1.

Subjects who qualify at the Baseline visit, based on inclusion/exclusion criteria, will be enrolled in the study and randomized in a 2:1 ratio within each site, to receive either 0.003% AR-15512 or AR-15512 vehicle to be administered BID as 1 drop in each eye for 12 months (365 days). Safety assessments will be conducted at each scheduled study visit. Systemic pharmacokinetic (PK) evaluation will be performed in a subset of subjects (n=35). Blood samples for systemic PK will be collected at the Baseline visit (Day 1) as well as the Day 14 and Day 90 visits [redacted] A summary of all study assessments per visit can be found in Appendix 1 (Schedule of Visits and Procedures).

Figure 1 Study Design



3.2 Rationale for Study Design and Control Group

Data from a Phase 2b trial with 369 subjects provides rationale for continued development of AR-15512 for the treatment of DED. [redacted] AR-15512 was found to be safe and well tolerated. With respect to study design, all pivotal clinical trials for topical ocular DED therapeutics approved in the United States have used vehicle as the comparator (Nichols 2021). This fact in combination with the efficacy and safety data from the Phase 2b trial fully support continued development of AR-15512 and the design of this long-term safety study.

3.3 Study Duration and Dates

The duration of subject participation is approximately 365 days (12 months).

4. STUDY POPULATION SELECTION

4.1 Study Population

This study is anticipated to enroll approximately 270 subjects with DED as defined below in Sections 4.2 and 4.3 so that approximately 108 subjects randomized to receive 0.003% and 54 subjects randomized to receive vehicle are expected to reach the Day 365 visit.
The anticipated dropout rate is 40%. To achieve this goal, approximately 360 subjects may be screened.

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to enter into the study:

1. Male or female, 18 years of age or older at the Baseline visit

2. Have a previous history of DED, clinician diagnosed or patient reported, within the previous 12 months of the Baseline visit

3. Have used or desired to use artificial tears for DED symptoms within 3 months prior to the Baseline visit

6. 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 the Baseline visit

7. Good general and ocular health, as determined by the investigator using medical history, ophthalmic examination and history, and vital signs (heart rate and blood pressure) at the Baseline visit

8. 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

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

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

4.3 Exclusion Criteria

Subjects meeting any of the following criteria during the Baseline visit will be excluded from entry into the study:

1. History or presence of any severe ocular disorder or condition (other than DED) in either eye that is, in the opinion of the investigator, likely to interfere with subject safety or evaluation, 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), which may interfere with vision (e.g., cataract, macular degeneration) or other disease which the investigator believes may interfere with study findings or interpretation

3. 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

4. Punctal or intracanalicular plug present in either eyelid at the Baseline visit or anticipated plug insertion or occlusion at any time during the study. If a subject had plugs, they must have been removed at least 14 days prior to the Baseline visit

5. History of ocular surgery within 6 months prior to the Baseline 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)

6. Have had a corneal transplant in either or both eyes

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

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

9. Use of artificial tears within 2 hours prior to the Baseline visit

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

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

12. Use of any other topical ocular medication not listed in Exclusions 8, 9, 10 or 11 within 24 hours prior to the Baseline visit.

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

14. 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 Baseline visit or anticipated use during the study

15. Use of a systemic medication containing an antihistamine within 24 hours prior to the Baseline visit

16. Use of lid heating therapy (i.e., LipiFlow®, iLUX®) or Meibomian gland probing/therapeutic expression within 6 months prior to the Baseline visit or anticipated during the study

17. Use of an investigational product or device within 30 days prior to the Baseline visit

18. Have received any vaccine within 3 days prior to the Baseline visit

19. At the Baseline visit, at the investigator's discretion, have uncontrolled or severe.

    a. Systemic allergy

    b. Rhinitis or sinusitis

20. 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 which would prevent or confound protocol-specified assessments (e.g. severe Sjögren's syndrome, severe rheumatoid arthritis, severe systemic lupus erythematosus, uncontrolled immunodeficiency disease, etc.)

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

22. Positive pregnancy test at the Baseline visit or currently breastfeeding or plans to become pregnant or breastfeed during the study

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

24. Randomization to a study arm in Phase 2b AR-15512-CS201 (COMET-1) study, Phase 3 AR-15512-CS301 (COMET-2) study or Phase 3 AR-15512-CS302 (COMET-3) study

25. 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

26. Employees directly involved in any prior or ongoing AR-15512 study at the clinical site

4.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. 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.

4.5 During Study Restrictions

4.5.1 Prior and Concomitant Therapy

Pharmacologic and non-pharmacologic therapies and surgeries/procedures will be queried as described in Section 6.3.

4.5.1.1 Prohibited Prior and Concomitant Therapies

The table below outlines all prohibited prior and concomitant therapies. Additional details can be found in the Supplemental Medication Guide. Subjects must discontinue the use of any of the therapies or interventions listed in Table 1 for the specified period prior to the Baseline visit and these therapies or interventions must not be used during the course of the study. Use of any of these therapies or interventions during the course of the study should be documented as a protocol deviation unless otherwise specified in a "Note" or Section 4.5.1.2.

Table 1 Required Washout Periods for Prohibited Prior and Concomitant Therapies

Treatment/Intervention	Washout Required Prior to the Baseline Visit
Use of any of topical ocular anti-inflammatory medication (e.g., ocular cyclosporine [Restasis®, Cequa™], lifitegrast [Xiidra®], any other prescription ophthalmic solution for DED, topical ocular corticosteroid- or non-steroidal-anti-inflammatory agents, topical ocular glaucoma or topical ocular IOP lowering medications)	30 days
Use of topical ocular autologous serum	30 days
Use of Tyrvaya™ (varenicline solution, nasal spray 0.03mg)	30 days
Use of any 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	30 days
Any investigational product or device	30 days
Lid-heating therapy, Meibomian gland probing, or therapeutic Meibomian gland expression	6 months
Contact lenses	7 days

4.5.1.2 Permitted Prior and Concomitant Therapies

Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. If the use of a specific therapy or intervention is in question, please contact Aerie according to the Medical Monitoring Plan.

Use of the following is permitted during the study:

- Artificial tears (must not be used within 2 hours prior to any study visit)
- Any other topical ocular medication (other than artificial tears) not itemized as an exclusion in Section 4.3 (**must not be used within 24 hours of any study visit**)
- Any systemic medication not itemized as an exclusion in Section 4.3 is permitted (**any systemic medication containing an antihistamine must not be used within 24 hours of any study visit**)
- Vaccines are permitted during the study provided that they are not administered within 3 days of any study visit
- Skin care products containing retinoids are permitted
- Lid hygiene (all forms) is permitted

4.5.2 Fluid and Food Intake

No requirements or restrictions.

4.5.3 Subject Activity Restrictions

Subjects are not to administer *their morning dose* of study intervention on Day 14, Day 90, Day 180, Day 270, and Day 365 (Exit visit). If a subject inadvertently doses their morning drop on the day of a clinic visit, at least 90 minutes must elapse between the time of drop administration reported by the subject and the start of the study visit. NOTE – If the subject is participating in the Systemic PK assessment and inadvertently doses their morning drop on the day of a clinic visit at either Day 14 or 90, then the visit needs to be rescheduled.

Subjects are not to administer artificial tears within 2 hours of any study visit

Subjects are not to administer any allowed topical ocular medication (other than artificial tears) within 24 hours of any study visit.

Subjects are not to administer any medication (topical or systemic) that includes an antihistamine within 24 hours of any study visit.

4.5.4 Women of Childbearing Potential and Acceptable Contraceptive Methods

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 acceptable effective method of contraception.

If a woman is of childbearing potential, she must have a pregnancy test performed at the visits specified in the Schedule of Visits and Procedures (Appendix 1). Additional pregnancy tests may also be required per local regulatory guidelines. Subjects with positive pregnancy test result must be excluded from the study. Enrolled subjects must agree to use an acceptable effective contraception method during the study.

Acceptable contraceptive methods when used consistently and in accordance with both the product label and the instructions of the physician (Clinical Trials Facilitation Group 2020), include:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)

2. Progestogen-only hormonal contraception (oral, injectable, or implantable)

3. Intrauterine device (IUD)

4. Intrauterine hormone-releasing system (IUS)

5. Bilateral tubal occlusion
6. Vasectomized partner[1]
7. Sexual abstinence[2]
8. Male or female condom with or without spermicide
9. Cap, diaphragm, or sponge with spermicide

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

4.5.4.1 Pregnancy Reporting

If pregnancy of a subject occurs during the study, the Investigator will notify the Sponsor within 24 hours of learning of the pregnancy. Any subject who becomes pregnant while participating in the study will discontinue study intervention.

Every attempt will be made to collect data on the pregnancy with subject/guardian permission. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

[1] Vasectomized partner is considered to be a highly effective birth control method providing that the partner is the sole sexual partner of the women of childbearing potential and that the vasectomized partner has received a medical assessment of the surgical success

[2] Sexual abstinence is considered to be an acceptable method of contraception when defined as refraining from heterosexual intercourse during the entire period of risk associated with the study interventions. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject

5. STUDY INTERVENTION

Study intervention is defined as any investigational product(s), marketed product(s), placebo, vehicle(s), or medical device(s) intended to be administered to a study participant according to the study protocol.

5.1 Description of Study Interventions

5.1.1 Investigational Product

AR-15512 ophthalmic solution is a sterile, preservative-free, isotonic, buffered aqueous solution containing 0.003% AR-15512, hypromellose, polyoxyl 35 castor oil, sodium dihydrogen phosphate dihydrate, and sodium chloride in water (either purified water or water for injection). The product formulations are adjusted to a pH of approximately 7 with sodium hydroxide and are packaged in blow-fill-seal containers of extruded polyethylene.

The investigational product will be provided in masked identical kits.

5.1.2 Vehicle (Control)

AR-15512 ophthalmic solution vehicle is a sterile, preservative-free, isotonic, buffered aqueous solution containing hypromellose, polyoxyl 35 castor oil, sodium dihydrogen phosphate dihydrate, sodium chloride in water (either purified water or water for injection). The product formulation is adjusted to a pH of approximately 7 with sodium hydroxide and is packaged in blow-fill-seal containers of extruded polyethylene.

AR-15512 vehicle will be provided in masked identical kits identical to the investigational product.

5.2 Selection and Timing of Dose for Each Patient

Subjects who qualify at the Baseline visit will be randomized into two groups, in a 2:1 ratio within each site, as follows:

- 0.003% AR-15512 (n = 180)
- AR-15512 vehicle (n = 90)

Subjects will be instructed to instill 1 drop of their randomized study intervention BID to both eyes 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).

At the Baseline visit (Day 1), as well as all follow up visits (Day 14, 90, 180, 270 and 365), the morning dose of randomized study intervention will be administered in clinic by study staff. All other doses will be administered by the subject. If a subject inadvertently doses their morning drop on the day of a clinic visit, at least 90 minutes must elapse between the

time of drop administration reported by the subject and the start of the study visit.
NOTE -- If the subject is participating in the Systemic PK assessment and inadvertently doses their morning drop on the day of a clinic visit at either Day 14 or 90, then the visit needs to be rescheduled.

5.3 Method of Assigning Patients to Study Intervention Groups

All subjects will be centrally assigned to randomized study intervention using interactive response technology (IRT). Before the study is initiated, the log-in information and directions for the IRT will be provided to qualified personnel at each site.

All qualified subjects will be randomized in a 2:1 ratio within each site to receive 0.003% AR-15512 or AR-15512 vehicle at the Baseline visit. The IRT will provide the site with the specific kit number(s) for each randomized subject at the time of randomization. Sites will dispense the study intervention according to the IRT instructions and the Schedule of Visits and Assessments (Appendix 1).

5.4 Masking

During the study, the investigator and site staff performing eligibility, safety, PK [redacted] assessments and the subjects will be masked. Subjects will be informed that there is a 1 in 3 chance they will receive vehicle.

AR-15512 (0.003%) and AR-15512 vehicle will be provided in identical single-use blow-fill-seal containers.

A randomization schedule for allocating the study interventions within a site will be prepared by an unmasked statistician who is not involved in the day-to-day conduct of the study.

The Sponsor clinical study team (e.g., personnel involved in day-to-day study management, monitors, data managers, and statisticians) will be masked.

5.5 Unmasking

Only in case of medical emergency or occurrence of adverse events that warrant unmasking in the opinion of the investigator, will the study intervention assignment(s) be unmasked and made available to the Investigator and the Medical Monitor. In the absence of medical need, the randomization code will not be available to the above personnel until after the study is completed and the database is locked.

If the Investigator feels it is necessary to unmask a subject's study intervention assignment after an emergency situation, the Investigator should contact the Medical Monitor or designee. The Medical Monitor will decide whether the study intervention for the subject should be unmasked. The study intervention assignment will be revealed on a subject-by-subject basis, thus leaving the masking on the remaining subjects intact.

5.6 Study Intervention Compliance

Study intervention compliance will be assessed by site records for treatments administered in the clinic. At all visits, the "morning" dose of randomized study intervention will be administered by the site staff. All other doses will be administered by the subject.

Subjects will be instructed on instillation and storage of study intervention at each visit (excluding the Exit visit), as well as provided written instructions.

Study compliance will be monitored by counting the number of returned unused vials compared to the total number of vials dispensed. The subject's unused study intervention vials will be collected throughout the study to assess dosing compliance.

If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of unused vials, then the subject will be deemed non-compliant and a protocol deviation must be recorded.

The study centers will keep an accurate accountability record that specifies the amount of study intervention dispensed to each subject, the amount of unused study intervention returned to the site, and the dates of each.

5.7 Packaging and Labeling

Each packaged unit will be labeled with an investigational label with the information required per applicable regulations.

The products for each study intervention assignment will be packaged into identical subject kits; each subject kit will contain one of 2 study interventions: 0.003% AR-15512 ophthalmic solution or AR-15512 ophthalmic solution vehicle.

Additional detail is provided in the Pharmacy Manual.

5.8 Storage and Dispensation

The study intervention must be dispensed or administered according to the procedures prescribed in this protocol and the Pharmacy Manual. Only qualified subjects may receive study intervention, in accordance with all the applicable regulatory requirements.
Only authorized staff is allowed to dispense these study interventions. Under normal conditions of handling and administration, the study interventions are not expected to pose significant safety risk to site staff. Adequate precautions must be taken to avoid direct contact with the study intervention. The study interventions will be stored in a secure area under the appropriate physical conditions for the product. Access to the study intervention will be limited to authorized site staff only. The study interventions will be stored as directed on the investigational label. The study interventions should be stored in clinic refrigerated (2°C to 8°C/36°F to 46°F) until dispensed to the subject. Temperature of the study intervention storage location at the site is to be monitored using a calibrated monitoring device and

documented. Study intervention should be removed from the refrigerator at least 30 minutes before use. At time of dispensing, the subject will be instructed to store the study intervention per details in the Pharmacy Manual and Subject Dosing Instructions. Study intervention should be protected from light (store in carton) as directed on the investigational label. Subjects should be instructed not to freeze the study intervention.

5.9 Accountability

5.9.1 Receipt and Disposition of Study Medication

Study intervention will be shipped to the Investigator's site from a central depot. If a discrepancy is noted, the appropriate individual at the Sponsor or designee must be notified immediately, in accordance with the Pharmacy Manual. The responsible person(s) for dispensing study intervention at the Investigator's site is the only site staff member permitted to distribute study intervention and also has sole responsibility to account for all returned unused vials of study intervention. The study intervention(s) must not be used outside this protocol. An Investigational Product Accountability Log will be kept at each clinical site.

5.9.2 Return of Study Intervention

When the study is completed or is terminated by the Sponsor, all unused study intervention kits / vials will be returned to the Sponsor or their designee. Subjects should be instructed to retain all unused vials of study intervention and return them to the clinical site starting with the Day 14 visit up to and including the Day 365 (Study Exit). 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 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 unused study intervention vials to the Sponsor or their designee.

6. STUDY PROCEDURES

6.1 Informed Consent

Prior to any study procedures, the study will be discussed with each subject, and subjects wishing to participate must give written informed consent. The verbal explanation of the study will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, may ask for more information. At the end of the interview, the subject should be given time to reflect. Subjects and/or a legally authorized representative then will be required to sign and date the ICF.

The ICF must have received approval/favorable review by a properly constituted Institutional Review Board (IRB) prior to use. A copy of the signed and dated consent document will be given to each subject. The original signed and dated ICF must be maintained in the study files at the Investigator's site.

The Investigator or staff is responsible for ensuring that no subject is exposed to any study related examination or activity before the subject has given written informed consent. It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, and should be notified that discontinuation from the study will not impact their subsequent care.

6.2 Demographics, Medical and Surgical History

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

6.3 Prior and Concomitant Medication Assessments

Any medication (including vaccines, over the counter, prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded. Prior medications taken within 90 days prior to the Baseline visit must also be recorded. Details regarding artificial tear use (if applicable), such as brand, frequency, start / end date will be recorded at each visit.

6.4 Vital Signs

Systolic and diastolic blood pressure will be measured using an appropriate sphygmomanometer after subjects have been at rest (seated) for at least 5 minutes. Blood pressure will be recorded in mmHg.

Heart rate will be measured using manual or automated methods in beats per minute (bpm) after the subject has been in a resting state (seated) for at least 5 minutes. If measured manually, pulse will be counted for 30 seconds, multiplied by 2, and recorded in bpm.

6.5 Clinical Laboratory Tests

6.5.1 Laboratory Parameters

A chemistry panel, a complete blood count (hematology and differential), and urinalysis will be performed as described in the Laboratory Manual.

6.5.2 Sample Collection, Storage and Shipping

The site staff responsible for collecting the laboratory samples will be identified on the Site Authorization and Delegation Log. Details for the preparation and shipment of samples and reference ranges will be provided in the Laboratory Manual.

6.5.3 Pregnancy Testing

Urine pregnancy tests for women of childbearing potential (WOCBP; defined in Section 4.5.4) are required at Baseline and Exit visits. Pregnancy tests must be negative for the subject to receive study treatment.

6.6 Systemic Pharmacokinetic Analysis

Blood draw for systemic pharmacokinetic measures will be performed at selected sites to include approximately 35 subjects. Given 2:1 randomization, this is expected to yield approximately 20 subjects exposed to AR-15512 and 10 subjects exposed to AR-15512 vehicle. Samples collected from subjects will be analyzed for AR-15512 concentration. Six blood samples per visit will be collected at Day 1, Day 14, and Day 90. On these visits, one PK sample will be collected pre-drop and 5 samples will be collected post-drop at the following time points: t=15 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours. Additional details of procedures are described in the Laboratory Manual.

6.7 Dispensing Study Intervention

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 IRT. The responsible study staff will account for all unused vials by maintaining an Investigational Product Accountability log.

See Table 2 for the study intervention dispensing schedule. Details of timing and procedures for dispensing study intervention are found in the Pharmacy Manual.

Table 2 Study Intervention Dispensing Schedule

Study Day	Quantity Dispensed to Subject
Day 1 (Baseline)	1 kit (40 vials)
14	2 kits (80 vials)
45	3 kits (120 vials)
90	3 kits (120 vials)
135	3 kits (120 vials)
180	3 kits (120 vials)
225	3 kits (120 vials)
270	3 kits (120 vials)
315	3 kits (120 vials)
365	Study Exit

6.8 Safety Assessments

6.8.1 Corrected Visual Acuity

Logarithmic minimum angle of resolution (LogMAR) visual acuity in both eyes will be assessed at all visits using an 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.

6.8.2 Best Corrected Visual Acuity

This assessment will only be performed at Baseline and Exit visit. Best Corrected Visual Acuity (BCVA) will be assessed by the ETDRS method. Subjects will have their visual acuity measured in a 4-meter lane under standard illumination by a certified examiner reading a standard ETDRS chart. Subjects will undergo manifest refraction at each visit. The visual acuity lane will be certified, as will the visual acuity examiner prior to study initiation. Specifications for the visual acuity lane, illumination, charts, light box, refraction lens, and the technician certification process are detailed in the Manual of Procedures.

6.8.3 Specular Microscopy to Assess Corneal Endothelial Cell Counts

Specular microscopy of the central cornea will be performed at the Baseline and Exit visit. Three images of the central corneal endothelium will be taken at each of the specified visits for each eye. Average cell density for each image will be generated by a built-in algorithm and recorded in the electronic case report forms (eCRFs). The overall average cell density of the central corneal endothelium will be calculated by electronic data capture (EDC) system. The presence or absence of abnormal cellular morphology (polymegethism) will be determined by visual inspection of images and noted in the eCRF. See the Manual of Procedures for additional details.

6.8.4 Biomicroscopy

Slit lamp biomicroscopy will be performed at all in-clinic study visits. 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:

- Cornea
- Conjunctiva
- Anterior Chamber
- Iris

- Lens
- Eyelid
- Anterior Vitreous

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

6.8.5 Ocular Surface Staining

Ocular surface staining will be performed at each visit, starting with sodium fluorescein staining of the cornea. Care should be taken when using sodium fluorescein strips to avoid causing ocular surface discomfort or irritation.

The subject should be instructed to look up such that 1 drop of sodium fluorescein can be applied to the right eye by gently pulling down on the lower lid and touching the droplet from a moistened (2 drops of normal sterile saline) strip onto the bulbar conjunctiva, releasing the droplet. The paper strip must not touch the bulbar conjunctiva. Repeat for the left eye with a new moistened strip. To thoroughly mix the sodium fluorescein with the tear film, the subject will be instructed to blink several times over approximately 15 seconds. Approximately 3 minutes after instillation of sodium fluorescein to both eyes, the entire corneal surface will be evaluated for sodium fluorescein staining, starting with the right eye. The examination will be performed with the slit lamp at approximately 16X magnification using the slit lamp's cobalt blue filter to illuminate the ocular surface and a yellow barrier filter placed directly in front of the objective lens of the slit lamp.

Grading of the resulting corneal staining will be based on the Oxford ocular grading scheme (cornea portion only) (Figure 2), which grades the entire cornea from 0 to 5. Half (0.5) grade increments may be used. The upper eyelid may be lifted slightly to visualize the entire corneal surface.

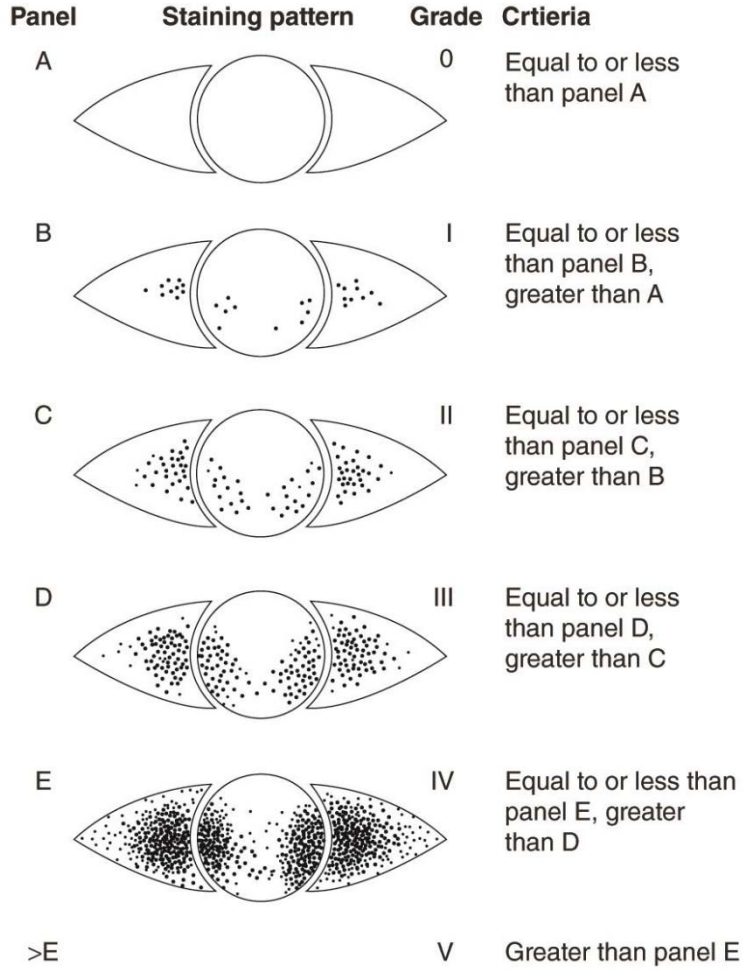
Following sodium fluorescein staining of the cornea, conjunctival staining with lissamine green will be performed as follows. Care should be taken when using lissmaine green strips to avoid causing ocular surface discomfort or irritation.

The subject should be instructed to look up such that 1 drop of lissamine green can be applied to the right eye by gently pulling down on the lower lid and touching the droplet from a moistened (2 drops of normal sterile saline) strip onto the bulbar conjunctiva, releasing the droplet. The paper strip must not touch the bulbar conjunctiva. Repeat for the left eye with a new moistened strip. To thoroughly mix the lissamine green with the tear film, the subject will be instructed to blink several times over approximately 15 seconds. Approximately 1 minute after instillation of lissamine green to both eyes and starting with the right eye, grading of the resulting conjunctival staining can begin. The 2 conjunctival regions (nasal and temporal) will each be graded (0 to 5) using the Oxford ocular grading scheme (Figure 2). Half (0.5) grade increments may be used. To grade the temporal zone, the subject should be instructed to look nasally; to grade the nasal zone, the subject should be

instructed to look temporally. The total conjunctival staining score is calculated as the sum of the 2 regions (maximum possible score 10).

Total ocular staining is then calculated as the sum of total corneal staining (0-5) and total conjunctival staining (0-10) for a **maximum possible score** of 15 per eye.

Figure 2 Oxford Ocular Grading Scheme



6.8.6 Intraocular Pressure

IOP must be measured only after the biomicroscopic exam is completed and must be measured prior to pupil dilation. IOP will be measured at all in-clinic study visits by qualified study site personnel with the subject seated. Every effort should be made to ensure that the same study site personnel uses the same device for IOP measurement for a given subject. A Goldmann applanation tonometer affixed to a slit-lamp is the preferred device for IOP measurement.

6.8.7 Dilated Fundus Exam by Slit Lamp

Dilated fundus exams will be performed at each visit using indirect ophthalmoscopy. The investigator will make observations of the vitreous, retina, macula, choroid and optic nerve.

Observations will be graded as Normal or Abnormal. Abnormal findings that are clinically significant (as determined by the investigator that may interfere with study parameters or otherwise confound the data) and those that are NCS will be described. An indirect Fundoscopy (peripheral retinal), examination should be performed if retinal disease is detected.

- Vitreous: Examination should emphasize the visual axis.
- Retina, Macula, Choroid: Include an observation of the retina and its blood vessels. Eyes should be excluded from the study if active inflammation is present.
- Optic Nerve: Significant damage or cupping to the optic nerve should be noted.

It is recommended that tropicamide 1% ophthalmic solution be used to dilate subjects.

[redacted]

[redacted]

6.10 Adverse Events Assessments

6.10.1 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

6.10.2 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. See Section 6.10.5.

- 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.

- Unexpected AE or unexpected AR: an AE or AR is considered "unexpected" if it is not listed in the 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, as amended. See Section 6.10.6.

6.10.3 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 AR is

unresolved at the time of exit, efforts will be made to follow up until the AE or AR 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 a treatment emergent adverse event (TEAE).

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

6.10.3.1 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 AEs. Such developments are recorded but are not reportable AEs. 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 AE, the Investigator is recommended to contact the Sponsor for guidance.

6.10.4 Severity

Severity of an AE is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an AE as determined by the Investigator or reported to them by the subject. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

1 = Mild: present and noticeable, but not distressing, and no disruption of normal daily activities

2 = Moderate: bothersome, discomfort sufficient to possibly reduce or affect normal daily activity

3 = Severe: incapacitating, with inability to work or perform normal daily activity

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 (see Section 6.10.8 for further information on SAEs, SARs, and suspected unexpected serious adverse reactions [SUSARs]).

6.10.5 Relationship

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.

6.10.6 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 SARs 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 6.10.2 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 (see Section 6.10.8).

6.10.7 Clinical Laboratory Adverse Events

Clinical laboratory values (other than pregnancy tests results) that are noted as abnormal and clinically significant at study exit and that are changes from Baseline values will be documented as AEs.

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

6.10.8.1 Reporting SAEs or SARs

An Investigator must immediately (i.e., within 24 hours) report any SAE or SAR (see Section 6.10.2 for definitions) to the Sponsor or its CRO representative, whether or not considered drug-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. The email or fax to submit the SAE report is found in Section 6.10.8.3.

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.

6.10.8.2 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 (Section 10.2) for the study and submit an SAE report form 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.

6.10.8.3 SAE Report Contact Information

[redacted]

[redacted]

6.11 Participant Discontinuation/Withdrawal from the Study

A subject may exit the study by their own volition or at the discretion of the Investigator or the Medical Monitor. Any subject may decide to voluntarily withdraw from the study at any time without prejudice.

The subject may also be discontinued from the study for the following reasons:

- AEs (AEs including, in the opinion of the Investigator, clinically relevant laboratory abnormalities, and intercurrent diseases reported by the subject or observed by the Investigator with documentation on the eCRF)
- Withdrawal of Consent
- Non-compliance (e.g., non-adherence to scheduled follow-up visits or use of study intervention)
- Lost to Follow-up
- Disallowed Concurrent Treatment
- Investigator Decision
- Protocol Deviation
- Death
- Other

6.11.1 Actions after Discontinuation

Also see Early Termination Procedures (Section 7.11).

All subjects who discontinue study intervention due to a report of an AE must be followed and provided appropriate medical care until their signs and symptoms have remitted or stabilized or until clinically meaningful abnormal laboratory findings have returned to acceptable or pre-study limits.

For subjects who choose to withdraw consent or who are discontinued for non-compliance prior to completing the study, every possible effort should be made by the Investigator to assure there is a final visit that includes all examinations listed for the Exit or Early Termination Visit.

6.11.2 Discontinuation of the Entire Study

The entire study may be discontinued at any given site by the Investigator the Sponsor / Sponsor representative, or at all sites by the Sponsor. Prompt, written notice of reasonable cause to all other relevant parties (Sponsor or Investigator) is required. Prompt notice to the IRB and to regulatory authorities is also required.

6.11.3 Completed Study

The study is completed when the last visit of the last subject has been completed at the last site taking part in the study. The Sponsor or Sponsor representative will be in communication with the investigational sites regarding enrollment completion.

7. STUDY ACTIVITIES

7.1 Day 1 (Baseline) Procedures

- Informed consent
- Demographics
- Medical, ophthalmic, and surgical history
- Prior and concomitant medication review
- Adverse events
- Vital signs (heart rate and blood pressure)
- Urine pregnancy test (women of child-bearing potential only)
- Corrected visual acuity
- Best corrected visual acuity
- Slit lamp biomicroscopy

- At least 5 minute rest
- Total ocular staining
- At least 10 minute rest
- Specular microscopy to assess corneal endothelial cell counts
- Inclusion and exclusion criteria review [redacted]
- Randomization
- Hematology, chemistry, and urinalysis (all subjects; all sites)
- Pre-dose blood draw for PK Samples (selected sites only)
- Dispensing of study intervention

[redacted]

- In-office administration of study intervention

[redacted]

- Post-dose blood draws for PK Samples (selected sites only)

[redacted]

- Intraocular pressure
- Dilated fundus exam

7.2 Day 14

- Collection of unused study intervention
- Concomitant medication review

- Adverse events
- Vital signs (heart rate and blood pressure)
- Corrected visual acuity
- Slit lamp biomicroscopy
- At least 5-minute rest
- Total ocular staining
- Pre-dose blood draw for PK Samples (selected sites only)
- Dispensing of study intervention
- In-office administration of study intervention
- Post-dose blood draws for PK Samples (selected sites only)
- Intraocular pressure
- Dilated fundus exam

7.3 Day 45

- Collection of unused study intervention
- Dispensing of study intervention

7.4 Day 90

- Collection of unused study intervention

- Concomitant medication review
- Adverse events
- Vital signs (heart rate and blood pressure)
- Corrected visual acuity
- Slit lamp biomicroscopy
- At least 5-minute rest
- Total ocular staining
- Pre-dose blood draw for PK Samples (selected sites only)
- Dispensing of study intervention
- [redacted]
- In-office administration of study intervention
- [redacted]
- Post-dose blood draws for PK Samples (selected sites only)
- [redacted]
- Intraocular pressure
- Dilated fundus exam

7.5 Day 135

- Collection of unused study intervention
- Dispensing of study intervention

7.6 Day 180

- Collection of unused study intervention

- Concomitant medication review
- Adverse events
- Vital signs (heart rate and blood pressure)
- Corrected visual acuity
- Slit lamp biomicroscopy
- At least 5-minute rest
- Total ocular staining
- Hematology, chemistry, and urinalysis
- Dispensing of study intervention

[redacted]

- In-office administration of study intervention

[redacted]

- Intraocular pressure
- Dilated fundus exam

7.7 Day 225

- Collection of unused study intervention
- Dispensing of study intervention

7.8 Day 270

- Collection of unused study intervention

- Concomitant medication review
- Adverse events
- Vital signs (heart rate and blood pressure)
- Corrected visual acuity
- Slit lamp biomicroscopy
- At least 5-minute rest
- Total ocular staining
- Dispensing of study intervention
- [redacted]
- [redacted]
- [redacted])
- In-office administration of study intervention
- [redacted]
- [redacted]
- [redacted]
- Intraocular pressure
- Dilated fundus exam

7.9 Day 315

- Collection of unused study intervention
- Dispensing of study intervention

7.10 Day 365

- Collection of unused study intervention
- Concomitant medication review
- Adverse events

- Vital signs (heart rate and blood pressure)
- Urine pregnancy test (women of child-bearing potential only)
- Corrected visual acuity
- Best corrected visual acuity
- Slit lamp biomicroscopy
- At least 5-minute rest
- Total ocular staining
- At least 10-minute rest
- Specular microscopy to assess corneal endothelial cell counts
- Hematology, chemistry, and urinalysis

[redacted]

- In-office administration of study intervention

[redacted]

- Intraocular pressure
- Dilated fundus exam
- Study exit

7.11 Early Termination

- Collection of unused study intervention

- Concomitant medication review
- Adverse events
- Vital signs (blood pressure and heart rate)
- Urine pregnancy test (women of child-bearing potential only)
- Corrected visual acuity
- Best corrected visual acuity
- Slit lamp biomicroscopy
- Specular microscopy to assess corneal endothelial cell counts
- Hematology, chemistry, and urinalysis
- Intraocular pressure
- Dilated fundus exam
- Study exit

8. QUALITY CONTROL AND ASSURANCE

The progress of the study will be monitored by on-site, written, and telephone communications between personnel at the Investigator's site and the Study Monitor. The Investigator will allow the Sponsor or designee and/or representatives of Health Regulatory Agencies to inspect all eCRFs, subject records (source documents), signed consent forms, study medication records (receipt, storage, preparation, and disposition), and regulatory files related to this study at mutually convenient times at regular intervals during the study and upon request after the study has been completed.

The purpose of these visits is to provide the Sponsor and/or Health Regulatory Agency the opportunity to evaluate the progress of the study, document compliance with the protocol and with regulatory requirements, verify the accuracy and completeness of subject eCRFs, resolve any apparent discrepancies or inconsistencies in the study records, and account for all investigational supplies.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

This is a study with safety assessments only and no formal comparisons will be made between 0.003% AR-15512 and vehicle.

All summaries will be presented by treatment group and visit as applicable. For assessments performed by eye, each eye will be summarized separately.

Quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. Qualitative variables will be summarized using counts and percentages.

For the purpose of summarization, medical history, concurrent therapies, and AEs will be coded to MedDRA and WHO Drug dictionaries, as appropriate.

Baseline measures are defined as the last non-missing measure prior to the initiation of randomized study treatment unless otherwise specified in the Statistical Analysis Plan (SAP). If a measure is taken both pre-drop and post-drop, baseline will be pre-drop Day 1 for all analyses. Change from baseline will be calculated as post-Baseline visit – Baseline.

9.2 Unit of Analysis

For assessments performed by eye, each eye will be summarized separately, and the eye will be the unit of analysis. For assessments performed by subject, the subject will be the unit of analysis.

9.3 Study Eye Selection

Study subjects will be dosed in both eyes. [redacted]

9.4 Missing Data

Safety analyses will be conducted using observed data only for the Safety Population. No data will be imputed.

9.5 Hypotheses

No formal statistical testing will be conducted in this long-term safety study. All inferential analysis conducted in the study will be for descriptive purposes only.

[redacted]

9.7 Determination of Sample Size

This is a phase 3 study to determine the long-term safety of 0.003% AR-15512. Approximately 270 subjects will be randomized in a 2:1 randomization ratio to receive 0.003% AR-15512 (180 subjects) or AR-15512 vehicle (90 subjects). Assuming a dropout

rate of 40%, approximately 108 subjects randomized to receive 0.003% and 54 subjects randomized to receive vehicle are expected to reach the Day 365 visit.

With 108 subjects completing 1 year on the investigational product, the study will have 96% probability to detect adverse events that occur at a true rate of 3% or greater. That is, with 108 subjects completing 1 year on the investigational product, if a specific AE is not observed, then with 96% confidence, that AE occurs at a true rate of < 3%.

9.8 Analysis Populations

9.8.1 Safety Population

The Safety Population includes all randomized subjects who have received at least one dose of the study intervention. The Safety Population will be analyzed for all safety assessments. Subjects in the Safety Population will be analyzed as treated.

[redacted]

9.9 Demographics and Baseline Characteristics

Subject demographics including age, sex, race, ethnicity, and iris color will be presented using summary statistics (mean, standard deviation, minimum, maximum, and median) or frequency counts and percentages as appropriate.

9.10 Safety Analysis

All safety analyses will be performed on the Safety Population.

AEs will be coded using the MedDRA dictionary. An AE is treatment emergent if it occurs or worsens on or after the date of the first dose of study treatment.

Frequencies and percentages of subjects with TEAEs will be summarized by system organ class and preferred term for the following categories of AEs:

- All AEs
- All TEAEs
- TEAEs at least possibly related to study treatment
- TEAEs leading to study treatment discontinuation
- Serious TEAEs

- Treatment-Emergent AESIs
- TEAEs by maximal severity
- TEAEs by study day of onset

Separate analyses will be performed for ocular and non-ocular AEs.

Other safety endpoints including vital signs, endothelial cell counts, laboratory parameters (hematology, chemistry, and urinalysis), corrected visual acuity, best corrected visual acuity, biomicroscopy, total ocular staining, IOP, and dilated fundoscopy will be summarized by treatment group and visit using descriptive statistics.

9.11 Analysis of Pharmacokinetic Data

Plasma pharmacokinetic parameters including AR-15512 area under the plasma concentration time curve (AUC), maximum recorded concentration (C_{max}), minimum recorded concentration (C_{min}), time of maximum concentration (T_{max}) will be summarized. R_{Cmax} and R_{AUC} (where R represents an accumulation factor) will be calculated. Details will be outlined in the SAP and Laboratory Manual.

9.13 Interim Analysis

An interim analysis will be conducted after all subjects have completed the Day 180 visit or discontinued. Details will be provided in the SAP.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators

The Principal Investigator must be a physician duly qualified to practice medicine and is responsible for all site medical-related decisions.

10.2 Medical Monitor

The Sponsor Lead shall serve as the primary point of contact for sites for all medical monitor queries. The Sponsor Lead will work with and / or elevate actions / site questions to the medical monitor, to ensure complete and accurate transfer of information, documentation of all queries and continued appropriate conduct of study. The Sponsor Lead contact information is:

The medical monitor should be contacted for urgent medical queries that require immediate (24 hour) response.

10.3 Institutional Review Board

This protocol, materials used to recruit subjects, and materials used to document consent must be approved by the IRB prior to initiation of the study. The name and address of each reviewing IRB will be documented in the Trial Master File for each participating country. Written IRB approval must adequately identify the protocol and informed consent. In addition to approving the protocol, the IRB must also approve the Subject Information and Consent Form, as well as any advertising tools that will be used for the study.

Written approval also must indicate whether approval was granted based on full committee review or expedited review. Copies of all approved materials, all correspondence with the IRB and written approval from the IRB must be made available to the Sponsor, prior to the start of subject enrollment into the study. The investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the

study. The investigator will submit written summaries of the study to the IRB as required. On completion of the study the IRB will be notified that the study has ended.

10.4 Ethical Conduct of the Study

The study will be conducted according to this clinical protocol and will be governed by all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not limited to:

- The approval of IRBs
- The Helsinki Declaration (World Medical Association 2013)
- US Code of Federal Regulations (CFR), Title 21
- International Conference on Harmonization (ICH) Consolidated Good Clinical Practice Guideline (E6 R2)
- Standard Operating Procedures (SOPs) of the Sponsor and any other vendors participating in the conduct of the study
- Obtaining prospective informed consent

10.5 Subject Information and Consent

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

All informed consent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB 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 the Sponsor prior to submission to the governing IRB 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 directed by the IRB.

10.6 Subject Confidentiality

The Investigator and his/her staff will maintain all personal subject data collected and processed for the purposes of this study using adequate precautions to ensure confidentiality, in accordance with local, state, and country laws and regulations.

Monitors, auditors and other authorized representatives of Aerie, the IRB approving this study, and government regulatory authorities (e.g., FDA) may be granted direct access to the study subject's original medical and study records for verification of the data or clinical study

procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

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

10.7 Study Monitoring

Clinical research associates will be responsible for monitoring the study sites and study activities. They will contact and visit the Investigator regularly. The actual frequency of monitoring visits depends on subject enrollment and on study site performance. Among others, the following items will be reviewed:

- Study progress
- Compliance with the protocol
- Completion of eCRFs
- Storage and accountability of study intervention
- Source data verification
- AE and SAE reporting
- Essential documents contained within the regulatory binder

For source data verification (i.e., comparison of eCRF entries with subject records), critical data points will be source verified and will include, but not be limited to: subject identification, informed consent and assent, if applicable (procedure, signature, and date), selection criteria, [redacted] and safety parameters (i.e., AEs). All other data will be subject to risk-based source verification, with specific details outlined in a Monitoring Plan.

10.8 Interactive Response Technology

Interactive response technology (IRT) is a validated touch-tone phone or web-based system that can be used for subject randomization/study intervention request, drug inventory management, emergency unmasking, and by study subjects for recording diary responses. IRT activities will be performed as described in the IRT User Manual.

10.9 Case Report Forms and Study Records

Investigators are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study data will be recorded via electronic CRFs (eCRFs). Each authorized study staff member will receive a unique access account in order to use the EDC system. Access accounts will not be shared among study staff. Authorized users will make entries and/or changes to the eCRF via a secure internet access. Each completed set of eCRFs will be reviewed by the Investigator who will then electronically sign and date the eCRF confirming that data for the subjects are complete and accurate.

Source document information should be legible. Recorded data should only be corrected by drawing a single line through the incorrect entry and writing the revision next to the corrected data. The person who has made the correction should place his or her initials as well as the date of the correction next to the correction. Data may not be obliterated by erasure, redaction, or with correction fluid.

The study records must include a copy of each Investigator's curriculum vitae, medical license, completed FDA Form 1572 / Statement of Investigator, each eCRF, subject charts/source documents, IB, protocol, protocol amendments, correspondence with the Sponsor and the IRB, study intervention storage, receipts, returns and dispensing records, Delegation of Responsibilities Log, site training records, records of site monitoring, unmasking documentation, AE and SAE reporting, IRB approvals, advertisements, written information provided to subjects, and subject completed ICFs. If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (e.g., Sponsor, other Investigator) who will accept the responsibility. Notice of this transfer, including written acceptance, must be made to and agreed upon by the Sponsor.

10.10 Protocol Deviations

Per ICH E6 (Good Clinical Practices [GCP]) R2 Section 4.5.1 the Investigator/institution should conduct the trial in compliance with the protocol agreed with the Sponsor and, if required, by the Regulatory Authority and which was given approval/favorable opinion by IRB.

Protocol waivers or deviations from the protocol inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The site will contact the Sponsor for clarification of inclusion and/or exclusion criteria as needed prior to enrollment of the study subject. The Sponsor or their representative will document clarification requests and responses. If a subject does not meet any of the eligibility criteria, that subject may not be enrolled into the study.

If the Investigator feels that in his/her clinical judgment, it is necessary to promptly implement reasonable alternatives to, or deviations from, the protocol in consideration of the safety of study subjects, the Sponsor is to be notified of these alternatives and deviations, and the reasons for such changes are to be documented in the study records. The Investigator is to also notify his/her IRB of any such changes.

If a significant protocol deviation is identified by the Investigator or through site monitoring activities an immediate submission to the IRB may be required e.g., 24 or 48 hours (as per IRB guidelines). The Sponsor will assess any protocol deviation and decide whether any of these non-compliances should be reported to the relevant competent authority as a serious breach of GCP and the protocol. If per the relevant competent authorities' requirements, the protocol deviation is not required to be reported immediately but is still required to be notified to the IRB, the specific protocol deviation will be added to the annual progress report.

The Sponsor will review and designate all protocol deviations prior to the database lock.

10.11 Access to Source Documentation

Monitors, auditors, and other authorized representatives of the Sponsor, the governing IRB(s), the FDA, the Department of Health and Human Services, European Medicines Agency, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical study procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

10.12 Data Generation and Analysis

A system of computerized data validation checks will be implemented and applied to the database on an ongoing basis. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and the Sponsor for resolution. The study database will be updated by the clinical investigator or their staff, in accordance with the resolved query reports. All changes to the study database will be documented.

Data will be checked per CRO's SOPs. The database will be locked, and a biostatistician will complete the analyses of the data in accordance with the Statistical Analysis Plan.

10.13 Retention of Data

The Investigator's site and clinical laboratory will retain all records related to the study in compliance with ICH Good Clinical Practices Guidelines E6 (R2) sections 4.9.4 and 4.9.5, and appliable local regulations.

Archived versions of the database will be saved by the Sponsor consistent with ICH Good Clinical Practices Guidelines E6 (R2) section 5.5.11, complying with whichever of the requirements is longer.

If for any reason custody of the records must be transferred, the Sponsor is to be notified in writing of any such transfer.

10.14 Financial Disclosure

The Principal Investigator and Sub-investigators (as listed on Form FDA 1572) will provide financial disclosure information prior to participation in the study. The Principal Investigator and any Sub-investigators will notify the Sponsor promptly of any required revision to their financial disclosure status (if applicable) during the term of this study, annually, or at the end of the study.

Under 21 CFR 54, the Investigator/Sub investigator is required to provide the Sponsor with sufficient accurate financial information to allow for complete disclosure or certification and to update this information if any relevant changes occur during the study and for one year following its completion.

10.15 Publication and Disclosure Policy

Study information for this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report.

Aerie Pharmaceuticals, as the Sponsor, has proprietary interest in the study. Authorship and manuscript composition will reflect joint cooperation between multiple Investigators and sites and Aerie Pharmaceuticals personnel. For studies with multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Aerie Pharmaceuticals.

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12. APPENDICES

Appendix 1 Schedule of Visits and Procedure

Visit	Baseline (Day 1)	Day 14	Day 45	Day 90	Day 135	Day 180	Day 225	Day 270	Day 315	Day 365 (Study Exit)	Early Termination
Visit Window (Days)	N/A	±2	±5	±5	±7	±7	±7	±7	±7	±7	N/A
Visit Type **C = Clinic** **D = Dispensing**	C	C	D	C	D	C	D	C	D	C	C
Informed consent	X										
Demographics	X										
Collection of unused study intervention		X	X	X	X	X	X	X	X	X	X
Medical, ophthalmic, and surgical history	X										
Prior or concomitant medication review	X	X		X		X		X		X	X
AE review[1]	X	X		X		X		X		X	X
Vital signs (heart rate and blood pressure)	X	X		X		X		X		X	X
Urine pregnancy test (WOCBP only)	X									X	X
Corrected visual acuity	X	X		X		X		X		X	X
Best corrected visual acuity	X									X	X
Slit lamp biomicroscopy	X	X		X		X		X		X	X
At least 5 min rest	X	X		X		X		X		X	
Total ocular staining (fluorescein staining of cornea and lissamine green staining of conjunctiva; Oxford grading scheme)	X	X		X		X		X		X	
At least 10 min rest	X									X	
Specular Microscopy to Assess Corneal Endothelial Cell Counts	X									X	X
Inclusion and exclusion criteria review[2]	X										
Randomization	X										
Hematology, chemistry, and urinalysis	X					X				X	X
Pre-dose Blood Draw for PK Samples (selected sites only)[3]	X	X		X							
Dispensing of study intervention	X	X	X	X	X	X	X	X	X		
[redacted]											

Visit	Baseline (Day 1)	Day 14	Day 45	Day 90	Day 135	Day 180	Day 225	Day 270	Day 315	Day 365 (Study Exit)	Early Termination
Visit Window (Days)	N/A	±2	±5	±5	±7	±7	±7	±7	±7	±7	N/A
[redacted]											
In-office administration of study intervention	X	X		X		X		X		X	
[redacted]											
Post-dose Blood Draws for PK Samples (selected sites only)[3]	X	X		X							
[redacted]											
Intraocular pressure	X	X		X		X		X		X	X
Dilated fundus exam	X	X		X		X		X		X	X
Study exit										X	X

Abbreviations: AE = adverse event; PK = pharmacokinetic; WOCBP = women of childbearing potential

[redacted]

[3] Pharmacokinetic evaluation will only be performed in a subset of subjects (n=35) at selected sites on visit Days 1, 14, and 90. Six plasma samples will be drawn at each of these visits as follows: pre-dose, and post dose at t=15 minutes, 30 minutes, 1 hour, 4 hours and 8 hours. Complete instructions are described in the Laboratory Manual.

[redacted]