A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease (COMET-3)

STUDY ID:

AR-15512-CS302

PROTOCOL

NCT05360966

Clinical Study Protocol

Study Title:	A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease (COMET-3)
Study Number:	AR-15512-CS302
Study Phase:	3
Product Name:	AR-15512
Indication:	Dry Eye Disease
Investigators:	Multicenter
Sponsor:	Aerie Pharmaceuticals, Inc.
Sponsor Contact:	4301 Emperor Blvd. Suite 400 Durham, NC 27703 +1-919-237-5300
[redacted]	
NCT #:	NCT05360966

	Date
Original Protocol (Rev 0):	9 May 2022
Amendment 1 (Rev 1)	12 May 2022
Amendment 2 (Rev 2)	4 May 2023

Confidentiality Statement

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease (COMET-3)

Study No: AR-15512-CS302

Original Protocol Date: 9 May 2022

Protocol Version No: Amendment 2

Protocol Version Date: 4 May 2023

[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 Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a **Co**ld Ther**m**or**e**ceptor Modula**t**or, for the Treatment of Dry Eye Disease (COMET-3)

Study Number:
AR-15512-CS302

Study Phase:
3

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

Study Design:
This will be a Phase 3, multicenter, vehicle-controlled, double-masked, randomized study conducted at approximately 20 sites in the United States. All subjects enrolled will have DED. The study will consist of Screening (Day -14) and Baseline (Day 1) visits as well as follow-up visits at Day 7, Day 14, Day 28, and Day 90 (Study Exit). In addition, there will be a Day 60 dispensing visit.

All subjects will be exposed to the Controlled Adverse Environment (CAE®) at the Screening visit to assess eligibility. At the end of the Screening visit, all qualified subjects will be assigned to administer AR-15512 vehicle BID to both eyes for approximately 14 days during the vehicle run-in period. After the vehicle run-in period, subjects will be re-evaluated at the Baseline visit for signs and symptoms of DED. Only subjects who requalify, based on inclusion/exclusion criteria, will be enrolled in the study and randomized in a 1:1 ratio within each site to receive 0.003% AR-15512 or AR-15512 vehicle to be administered BID as 1 drop in each eye for 90 days. Efficacy will be assessed at the Baseline (Day 1) visit and Day 7, Day 14, Day 28, and Day 90. At the end of the Day 90 visit, subjects will exit the study. Safety assessments will be conducted at each study visit.

Study Population:
This study is anticipated to enroll approximately 460 subjects with DED so as approximately 414 subjects complete Day 90. The anticipated dropout rate is 10%. To achieve this goal, approximately 1500 subjects may be screened.

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

- Male or female, 30 years of age or older at the Screening visit
- Have a previous history of DED, clinician diagnosed or patient reported, within the previous 6 months prior to the Screening visit
- Have used and/or desired to use artificial tears for DED symptoms within 2 months prior to the Screening visit
- Both of the following signs of DED in the same eye:
    a. Total corneal fluorescein staining score of ≥ 2 and ≤ 15 based on the modified NEI grading scheme, with no one region scoring > 3 in at least 1 eye at the Screening visit only

b. Anesthetized Schirmer test score ≥ 2 and < 10 mm/5 min in at least 1 eye and the same eye must qualify at both Screening and Baseline visits

- A score of ≥ 50 based on Ocular Discomfort Score (ODS) assessed on a Visual Analog Scale (VAS) at both the Screening and Baseline visits
- A score of ≥ 50 based on SANDE (Symptoms Assessment iN Dry Eye) at both the Screening and Baseline visits
- Increase in the signs and symptoms of DED based on the CAE exposure at the Screening visit only demonstrated by:
  a. ≥ 1-point increase in inferior region corneal staining score (assessed using sodium fluorescein staining) in at least 1 eye based on the Ora Calibra® grading scale after the 90-minute CAE® exposure
  b. Ora Calibra ODS score ≥ 3 at 2 or more consecutive time points in at least 1 eye during CAE® exposure within ≤ 20 minutes of entering the CAE® (if a subject has an ocular discomfort rating of 3 at time 0 for an eye, the subject must report an ocular discomfort rating of 4 for 2 consecutive measurements for that eye within ≤ 20 minutes of entering the CAE)
- Corrected visual acuity equal to or better than logMar +0.7 (Snellen equivalent equal to or better than 20/100), as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at both the Screening and Baseline visits

Key Exclusion Criteria

Subjects meeting any of the following criteria during the Screening and/or Baseline visits (i.e., qualification visits) will be excluded from entry into the study:

- History or presence of any ocular disorder or condition (other than DED) in either eye that would, in the opinion of the investigator, interfere with the interpretation of the study results or subject safety, such as: significant corneal or conjunctival scarring; pterygium or nodular pinguecula; conjunctivitis, or inflammation not associated with DED; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; evidence of keratoconus; etc. (Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed.)
- 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
- History of ocular surgery within 1 year prior to the Screening visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision)
- Have had a corneal transplant in either or both eyes
- Use of contact lenses in either eye within 7 days prior to the Screening visit or planned use during the study
- Punctal or intracanalicular plug present in either eyelid within 14 days prior to the Screening visit or anticipated plug insertion or occlusion at any time during the study
- Regular use of lid hygiene within 14 days prior to the Screening visit or any planned use during the study
- Use of lid heating therapy (i.e., LipiFlow®, iLUX®, TearCare®) or Meibomian gland probing/therapeutic expression within 1 year prior to the Screening visit or anticipated during the study
- Use of artificial tears within 2 hours prior to the Screening visit or anticipated use during the study
- Use of any topical ocular anti-inflammatory medication within 30 days prior to the Screening 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, or autologous serum

- Use of any topical ocular glaucoma medication within 30 days prior to the Screening visit or anticipated use during the study
- Regular use of any other topical ocular medication within 14 days prior to the Screening visit or anticipated use during the study (e.g., eye whitening products [Visine®, Lumify®], topical ocular antibiotics, topical ocular antihistamines, mast cell stabilizers, age-related blurry near vision (presbyopia) drops [Vuity™], or other over-the-counter [OTC], herbal, prescription, or nutritional supplements). Note: Occasional short-term use of these topical ocular medications will be permitted provided that no drops were used within 24 hours of the Screening visit or anticipated use within 24 hours of any study visit
- Use of Tyrvaya™ (varenicline solution, nasal spray 0.03mg) within 30 days prior to the Screening 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 Screening visit or anticipated use during the study
- Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) less than 14 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Occasional short-term use of medications such as systemic antihistamines will be permitted provided that use was not within 24 hours of the Screening visit or anticipated use within 24 hours of any study visit
- Initiation, discontinuation, or change in dose of a systemic corticosteroid less than 60 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Non-ocular topically applied corticosteroids (including topical creams, nasal sprays and inhalers) will be permitted during the study and the dose is not required to be stable
- Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) less than 60 days prior to the Screening visit or a change in dosage is anticipated during the study

Study Interventions and Dosing Regimens:

Vehicle Run-in Period

- Topical ocular administration of one drop of AR-15512 vehicle in both eyes BID

Randomized Intervention Period (1:1)

- 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 15 weeks (2 weeks of vehicle run-in period followed by 13-week randomized intervention period)

Efficacy Assessments:

Primary Assessments:

- Unanesthetized Schirmer test

Secondary Assessments:

- SANDE (Symptom Assessment iN Dry Eye) Questionnaire Score
- Ocular Discomfort Score (ODS) - Visual Analog Scale (VAS)
- Eye Dryness Score based - VAS

[redacted]

[redacted]

Safety Assessments:

- Vital signs (heart rate and blood pressure)
- Hematology, chemistry, and urinalysis
- Adverse events
- Corrected visual acuity
- Intraocular pressure
- Dilated fundus exam

Statistical Methods:

Sample Size Determination

Two hundred two (202) intention-to-treat (ITT) population subjects (study eyes) per treatment group yields 99% power to conclude superiority of 0.003% AR-15512 over vehicle in the proportion of subjects ≥ 10 mm in unanesthetized Schirmer score on Day 14, assuming a true difference of proportions (AR-15512 vs vehicle) of 80% vs 30% and a two-sided alpha = 0.05.

Additionally, 202 ITT population subjects (study eyes) per treatment group yields 99% power to conclude superiority of 0.003% AR-15512 over vehicle in the mean change from Baseline in SANDE score on Day 28 assuming a true difference (AR-15512 minus vehicle) of -7.9, a common standard deviation of 17.72, and a two-sided alpha = 0.05.

Accounting for subject discontinuations, approximately 460 total subjects (230 per treatment arm) will be randomized assuming a dropout rate of 10%.

Primary endpoint

- Proportion of subjects ≥ 10 mm increase in unanesthetized Schirmer score on Day 14

Secondary endpoints

- Change from Baseline in SANDE score on Day 28
- Change from Baseline in unanesthetized Schirmer score on Day 14

[redacted]

- Change from Baseline in SANDE Score on Day 90
- Change from Baseline in ODS - VAS on Day 90
- Change from Baseline in Eye Dryness - VAS Day 90

[redacted]

[redacted]

- Proportion of subjects ≥ 10 mm increase in unanesthetized Schirmer score on Day 90
- Change from Baseline in unanesthetized Schirmer score on Day 90

[redacted]

Statistical Analyses

Analysis of primary efficacy will be based on difference of proportions tests for dichotomous endpoints and analysis of covariance (ANCOVA) for change from Baseline endpoints. Available data only will be used if the discontinuation rate is < 5% in each arm; otherwise, an estimand based on multiple imputation will be used for the primary analysis.

Analysis of secondary efficacy will be conducted as described for the primary efficacy endpoints, using difference of proportions tests or ANCOVA with available data only if the discontinuation rate is < 5% in each arm and multiple imputation otherwise. The secondary efficacy endpoints will only be formally tested if the endpoint is significant at the α=0.05 level. Testing of the secondary efficacy endpoints will be conducted using a fixed-sequence hierarchical strategy.

Date of Original Approved Protocol (Rev 0): 9 May 2022

Date of Most Recent Protocol Amend (Rev 2): 4 May 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ANCOVA	Analysis of Covariance
AE	Adverse Event
AR	Adverse Reaction
BID	Twice Daily
CAE	Controlled Adverse Environment
CFB	Change From Baseline
CFR	Code of Federal Regulations
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
DED	Dry Eye Disease
DHHS	Department of Health and Human Services
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
EDS	Eye Dryness Score
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRAS	Generally Recognized as Safe
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intrauterine Device

IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
LOCF	Last Observation Carried Forward
LOGMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Square
NCS	Not Clinically Significant
[redacted]	
ODS	Ocular Discomfort Score
OTC	Over-the-Counter
OD	Right Eye
OS	Left Eye
OU	Both Eyes
PP	Per Protocol
[redacted]	
SAE	Serious Adverse Event
SANDE	The Symptom Assessment Questionnaire iN Dry Eye
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	
TEAE	Treatment Emergent Adverse Event
TID	Three Times Daily
TRPM8	Transient Receptor Potential Melastatin 8
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHO	World Health Organization
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(s)

To evaluate the safety and efficacy of topical ophthalmic 0.003% AR-15512 compared to its vehicle administered BID in subjects with DED.

3. INVESTIGATIONAL PLAN

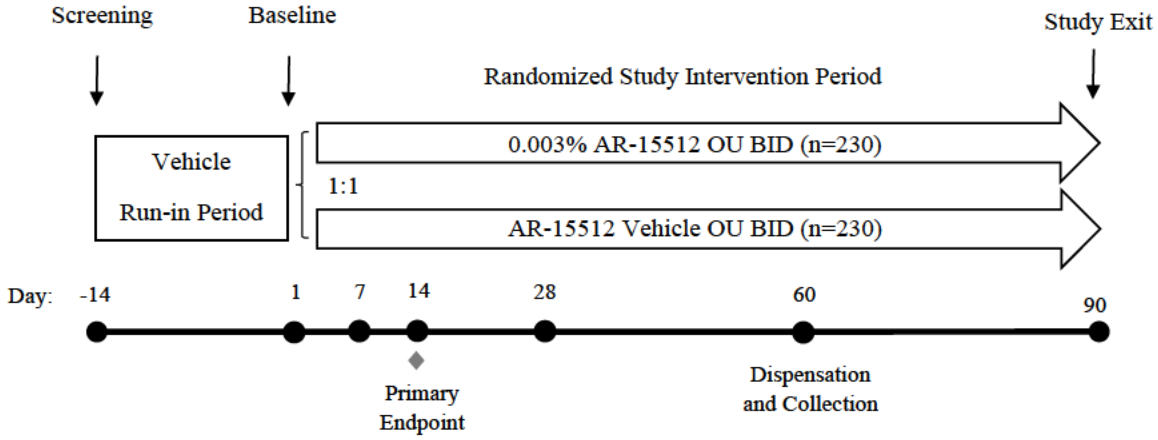
3.1 Overall Study Design and Plan

This will be a Phase 3, multicenter, vehicle-controlled, double-masked, randomized study conducted at approximately 20 sites in the United States. All subjects enrolled will have DED. The study will consist of Screening (Day -14) and Baseline (Day 1) visits as well as follow-up visits on Day 7, Day 14, Day 28 and Day 90 (Study Exit). There will also be a

Day 60 dispensing visit. All subjects will be exposed to the Controlled Adverse Environment (CAE®) at the Screening visit to assess eligibility.

At the end of the Screening visit, all qualified subjects will be assigned to administer AR-15512 vehicle BID (approximately 7:00h - 10:00h and 19:00h - 22:00h) to both eyes for approximately 14 days during the vehicle run-in period. After the vehicle run-in period, subjects will be re-evaluated at the Baseline visit for signs and symptoms of DED. Only subjects who requalify, based on inclusion/exclusion criteria, will be enrolled in the study and randomized in a 1:1 ratio within each site to receive 0.003% AR-15512 or AR-15512 vehicle to be administered BID (approximately 7:00h - 10:00h and 19:00h - 22:00h) as 1 drop in each eye for 90 days. Efficacy will be assessed at the Baseline (Day 1) visit and Days 7, 14, 28 and 90. At the end of the Day 90 visit, subjects will exit the study. Safety assessments will be conducted at each study visit. A summary of all study assessments per visit can be found in Appendix 1 (Schedule of Visits and Procedures).

Figure 1 Study Design Diagram



3.2 Rationale for Study Design and Control Group

Data from a similarly designed 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.

These data and the fact that all pivotal clinical trials for topical ocular DED therapeutics approved in the United States and Europe have used vehicle as the comparator (Nichols 2021), fully support Phase 3 study design.

3.3 Study Duration and Dates

The duration of subject participation is approximately 15 weeks (2 weeks vehicle run-in period before randomization followed by 13 weeks of randomized study intervention administration).

4. STUDY POPULATION SELECTION

4.1 Study Population

This study is anticipated to enroll approximately 460 subjects with DED as defined below in Sections 4.2 and 4.3 so as approximately 414 subjects complete Day 90. The anticipated dropout rate is 10%. To achieve this goal, approximately 1500 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, 30 years of age or older at the Screening visit
2. Have a previous history of DED, clinician diagnosed or patient reported, within the previous 6 months prior to the Screening visit
3. Have used, and/or desired to use artificial tears for DED symptoms within 2 months prior to the Screening visit

8. Corrected visual acuity equal to or better than logMar +0.7 (Snellen equivalent equal to or better than 20/100), as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at both the Screening and Baseline visits
9. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
10. Written informed consent from the subject has been obtained prior to any study related procedures
11. Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits

4.3 Exclusion Criteria

Subjects meeting any of the following criteria during Screening and/or Baseline visits (i.e., qualification visits) will be excluded from entry into the study:

1. History or presence of any ocular disorder or condition (other than DED) in either eye that would, in the opinion of the investigator, interfere with the interpretation of the study results or subject safety, such as: significant corneal or conjunctival scarring; pterygium or nodular pinguecula; conjunctivitis, or inflammation not associated with DED; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; evidence of keratoconus; etc. (Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed.)
2. Current evidence of other significant ophthalmic disease requiring topical medication (e.g. glaucoma or 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. History of ocular surgery within 1 year prior to the Screening visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision)
5. Have had a corneal transplant in either or both eyes
6. Use of contact lenses in either eye within 7 days prior to the Screening visit or planned use during the study
7. Punctal or intracanalicular plug present in either eyelid at the Screening 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 screening visit
8. Regular use of lid hygiene within 14 days prior to the Screening visit or any planned use during the study
9. Use of lid heating therapy (i.e., LipiFlow®, iLUX®, TearCare®) or Meibomian gland probing/therapeutic expression within 1 year prior to the Screening visit or anticipated during the study
10. Use of artificial tears within 2 hours prior to the Screening visit or anticipated use during the study
11. Use of any topical ocular anti-inflammatory medication within 30 days prior to the Screening visit or anticipated use during the study (e.g., ocular cyclosporine [Restasis®, Cequa™], lifitegrast [Xiidra®], any other prescription ophthalmic product for DED, topical ocular corticosteroid- or non-steroidal-anti-inflammatory agents, or autologous serum
12. Use of any topical ocular glaucoma medication within 30 days prior to the Screening visit or anticipated use during the study
13. Regular use of any other topical ocular medication (i.e., in addition to medications excluded by exclusion criterion #11 or #12) within 14 days prior to the Screening visit or anticipated use during the study (e.g., eye whitening products [Visine®, Lumify®], topical ocular antibiotics, topical ocular antihistamines, mast cell

stabilizers, age-related blurry near vision (presbyopia) drops [Vuity™], or other over-the-counter [OTC], herbal, prescription, or nutritional supplements). Note: Occasional short-term use of these topical ocular medications will be permitted provided that no drops were used within 24 hours of the Screening visit or anticipated use within 24 hours of any study visit

14. Use of Tyrvaya™ (varenicline solution, nasal spray 0.03mg) within 30 days prior to the Screening visit or anticipated use during the study
15. Use of medications for the treatment of severe DED and/or Meibomian gland disease such as oral pilocarpine, oral cevimeline, oral macrolides, oral tetracyclines, oral tetracycline derivatives, and oral retinoids within 30 days prior to the Screening visit or anticipated use during the study
16. Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) less than 14 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Occasional short-term use of medications such as systemic antihistamines will be permitted provided that use was not within 24 hours of the Screening visit or anticipated use within 24 hours of any study visit
17. Initiation, discontinuation, or change in dose of a systemic corticosteroid less than 60 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Non-ocular topically applied corticosteroids (including topical creams, nasal sprays and inhalers) will be permitted during the study and the dose is not required to be stable
18. Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) less than 60 days prior to the Screening visit or a change in dosage is anticipated during the study
19. Have received any vaccine within 3 days prior to the Screening or Baseline visit
20. Use of an investigational product or device within 30 days prior to the Screening visit
21. Randomization to a study arm (active or vehicle) in the Phase 2b AR-15512-CS201 (COMET-1) study, the Phase 3 AR-15512-CS301 (COMET-2) or the Phase 3 AR-15512-LTSS (COMET-4) studies or in the active arm in the Phase 1 21-110-A study
22. At the Screening visit, at the investigator's discretion, have uncontrolled or severe:
    a. Systemic allergy
    b. Rhinitis or sinusitis
23. History or presence of significant systemic disease (i.e.: cardiovascular, pulmonary, hepatic, renal, hematologic, immunologic). Significant is defined as any disease that, in the assessment of the Investigator, would put the safety of the subject at risk through participation, or 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.)
24. Known allergies or sensitivity to the study interventions or study diagnostic agents including sodium fluorescein, lissamine green, etc.

25. Positive pregnancy test at Screening or Baseline visits or currently breastfeeding or plans to become pregnant or breastfeed during the study
26. Women of childbearing potential who are not using a medically acceptable form of birth control
27. 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
28. Employees directly involved in the AR-15512-CS302 trial 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 Sections 6.3 and 6.2.

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 Screening 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 must be documented as a protocol deviation unless otherwise specified in a "Note" or Section 4.5.1.3.

4.5.1.2 Prior and Concomitant Therapies Requiring Stability

Table 2 below outlines all prior and concomitant therapies requiring stability. Additional details can be found in the Supplemental Medication Guide. Subjects using these therapies prior to the study must have been on a stable dose or treatment for the time period specified in the table. Initiation, change in dose, or discontinuation of any of these therapies during the study must be documented as a protocol deviation unless otherwise specified in a "Note" or Section 4.5.1.3.

Table 2 Prior and Concomitant Therapies Requiring Stability

Treatment/Intervention	Required Period of Stability Prior to the Screening Visit
Any systemic medication known to cause ocular drying (e.g., antihistamines, tricyclic antidepressants) *Note: Occasional short-term use of medications such as systemic antihistamines will be permitted provided that use was not within 24 hours of any Study visit*	14 days[1]
Systemic immunomodulators (e.g., hydroxychloroquine, methotrexate, cyclosporine)	60 days[1]
Systemic corticosteroids (e.g., IV and oral)	60 days[1]

[1] The use of these medications is allowed during the study provided that the dosing regimen is stable for the time specified in the table (prior to the Screening visit). The total time for washout if one of these medications is discontinued prior to the Screening visit is the same duration required for stability.

4.5.1.3 Permitted Prior and Concomitant Therapies

Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. Additional details can be found in the Supplemental Medication Guide. If the use of a specific therapy or intervention is in question, please contact Aerie (see Section 10.2).

Use of the following is permitted during the study:

- Any systemic medication not itemized as an exclusion in Section 4.3 is permitted.
- Occasional (as needed) use of medications such as non-prescription anti-inflammatories / pain relievers (e.g. aspirin, acetaminophen etc.), and acid-reflux/heartburn medications will be permitted.
- Occasional short-term use of medications such as systemic antihistamines will be permitted **but should be discouraged. Use is not allowed within 24 hours of any Study visit**
  - For example, as needed (short-term) use of and cold/flu medications that **do not** contain antihistamines is permitted and these medications are preferred. Cold/flu medications that **do** contain antihistamines are discouraged but will be permitted (please refer to the Prohibited and Permitted Concomitant Medication List).
- Vaccines are permitted during the study provided that they are not administered within 3 days of any study visit
- Occasional short-term use of topical ocular medications not described in exclusion criteria #11 and #12 are permitted
  - Examples of topical ocular medications that may be used on an occasional short-term bases include: eye whitening products [Visine®, Lumify®], topical ocular antibiotics, topical ocular antihistamines, mast cell stabilizers or other OTC, herbal, prescription, or nutritional supplements
  - **These topical ocular medications must not be used within 24 hours of any study visit**

    - Although occasional short-term use is permitted, use of these **topical ocular medications should be discouraged**
- Non-ocular topical or other (non-ocular) locally acting corticosteroids (e.g., topical creams, nasal sprays, inhalers etc.) are permitted.
- Skin care products containing retinoids are permitted.

4.5.2 Fluid and Food Intake

No requirements or restrictions.

4.5.3 Subject Activity Restrictions

Subjects are not to administer the evening dose of the randomized study intervention on Days 1, 7, 14, 28 and 90 since this dose will be administered during the clinic visit instead.

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. Subjects with negative pregnancy test 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 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.

5. STUDY INTERVENTIONS

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.

[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

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 Screening visit will be instructed on proper administration procedure to instill 1 drop of AR-15512 vehicle BID to both eyes on Days -14 to -1 (vehicle run-in period) 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).

Following the vehicle run-in period, those subjects who requalify at the Baseline visit, will be randomized into two groups, in a 1:1 ratio within each site, as follows:

- 0.003% AR-15512 (n = 230)
- AR-15512 vehicle (n = 230)

Subjects will be re-instructed on proper administration procedures at the Baseline visit. Subjects will be instructed to administer 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 Screening visit, the morning dose of AR-15512 vehicle will be administered in clinic by the subject under site staff supervision. At the Day 1, Day 7, Day 14, Day 28 and Day 90 visits, the “evening” (or second) dose of randomized study intervention will be administered by the site staff, thus there will be no “evening” (or second) dose administered by the subjects on these days. All office visits must be arranged at approximately the same time of day ± 1 hour.

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 assigned to receive AR-15512 vehicle BID to both eyes for approximately 14 days during the vehicle run-in period. Following the run-in period, all subjects who requalify at the Baseline visit (Day 1), will be randomized in a 1:1 ratio, within each site, to receive 0.003% AR-15512 or AR-15512 vehicle. 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 vehicle run-in period, the subject will be masked. During the randomized study intervention period, the investigator and site staff performing eligibility / efficacy and safety assessments and the subjects will be masked. Subjects will remain masked during the randomized phase. Subjects will be informed that they all will receive vehicle at some point in the study, but the exact timing will not be specified.

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

5.5 Unmasking

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.

Study intervention assignments will be masked to the Investigator, the clinical study team (Sponsor, personnel involved in day-to-day study management, Monitors, Data Managers, and Statisticians), and the subjects. 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. Only after consultation with the Medical Monitor will a decision be made as to whether or not 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

At the Screening visit, the morning dose will be administered in clinic by the subject under supervision from site personnel. For the Day 1, Day 7, Day 14, Day 28 and Day 90 visits, the "evening" dose will be administered by designated site personnel; all other doses will be administered by the subject. Study intervention compliance will be assessed by site records for these treatments.

The subjects' used and unused study intervention vials will be collected at each visit from the Baseline visit up to and including the Day 90 (Exit) visit to assess dosing compliance. Dosing compliance will be based off the used and unused vial count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of used and unused vials, then the subject will be deemed non-compliant and a protocol deviation must be recorded. Subjects will be instructed on instillation and storage of study intervention at the end of each visit (excluding the exit visit), as well as provided written instructions.

These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

The study centers will keep an accurate accountability record that specifies the amount of study intervention dispensed to each subject, the amount of 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 randomized intervention kits; each randomized intervention 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

The study intervention must be dispensed and administered according to the procedures prescribed in this protocol and 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 must 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 to protect 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 interventions 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(s) permitted to distribute study intervention and also has sole responsibility to account for all returned used, partially used and 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 study materials including used and unused study intervention kits / vials will be returned to the Sponsor or their designee. Subjects should be instructed to retain all vials (used, partially used or unused) of study intervention and return them to the clinical site. All study intervention accounting procedures must be completed before the study is considered to be concluded.
The responsible person(s) at the Investigator's site has the sole responsibility to account for all used, partially used, and unused study intervention. This site staff member at the Investigator's site will complete a study intervention returns form or equivalent that will be signed by the Investigator or designee prior to returning the used and unused study intervention vials to the Sponsor or their designee.

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 Screening 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, OTC, prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded. Prior medications taken up to at least 90 days prior to the Screening visit must also be recorded. Additional details on prohibited and allowable medications can be found in the Supplemental Medication Guide.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

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

6.4.2 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.

6.4.3 Pregnancy Testing

Urine pregnancy tests for women of childbearing potential (WOCBP; defined in Section 4.5.4) are required at Screening, Baseline and Day 90 (Study Exit) visits. Pregnancy tests must be negative for the subject to receive study intervention.

6.5 Dispensing Study Intervention

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

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 used, partially used and unused study kits / vials by maintaining a Study Intervention Accountability log.

See Table 3 for the study intervention dispensing schedule. Details of timing and procedures for dispensing study intervention are found in the Pharmacy Manual.

Table 3 Study Intervention Dispensing Schedule

Study Day	Quantity Dispensed to Subject
-14	1 Run-In kit (40 vials)
1	1 Randomized Intervention Kit (40 vials)
7	1 vial administered in-office from the Day 7 Kit
14	1 Randomized Intervention Kit (40 vials)
28	2 Randomized Intervention Kits (80 vials)
60[1]	2 Randomized Intervention Kits (80 vials)
90	Study Exit

[1] Dispensation and collection of study intervention only. No other procedures are scheduled on this day.

6.6 Efficacy Assessments

6.6.1 Symptom Questionnaire (Visual Analog Scale (VAS))

Subjects will be asked to rate each of the following DED symptoms (both eyes together), over the last 24 hours, each on a separate VAS: *ocular discomfort (ODS), eye dryness (EDS),* [redacted] For each VAS, subjects will be asked to place a vertical mark on the horizontal line to indicate the level of each symptom, with 0 corresponding to "no symptom" and 100 corresponding to "maximal symptom". The assessment line length of each scale will be 100 mm (Figure 2). Instructions for measuring each subject's response on each VAS can be found in the Manual of Procedures.

Figure 2 Ocular Discomfort: Visual Analog Scale

Eye Dryness: Visual Analog Scale

[redacted]

6.6.2 Symptom Assessment in Dry Eye Questionnaire

The SANDE questionnaire (Schaumberg 2007) is comprised of 2 unique VASs to assess the frequency and severity of DED symptoms. Subjects will be asked to complete the SANDE to rate both the frequency and severity of DED symptoms for both eyes together. Each of the two questions will be accompanied by a VAS. The assessment line length of the scale will be 100 mm and will be similar to the following depiction (Figure 3). Higher scores indicate greater frequency or severity.

Instructions for measuring each subject's response on each VAS can be found in the Manual of Procedures. The SANDE score will be calculated by multiplying the frequency score by the severity score and obtaining the square root. The final value must be rounded to the nearest whole number.

Figure 3 SANDE Questionnaire

PLEASE COMPLETE THE FOLLOWING QUESTIONS REGARDING THE FREQUENCY AND SEVERITY OF YOUR DRY EYE SYMPTOMS:

1. **Frequency of symptoms:**

   Place a single vertical mark on the horizontal line to indicate how often, on average, your eyes feel dry and/or irritated.

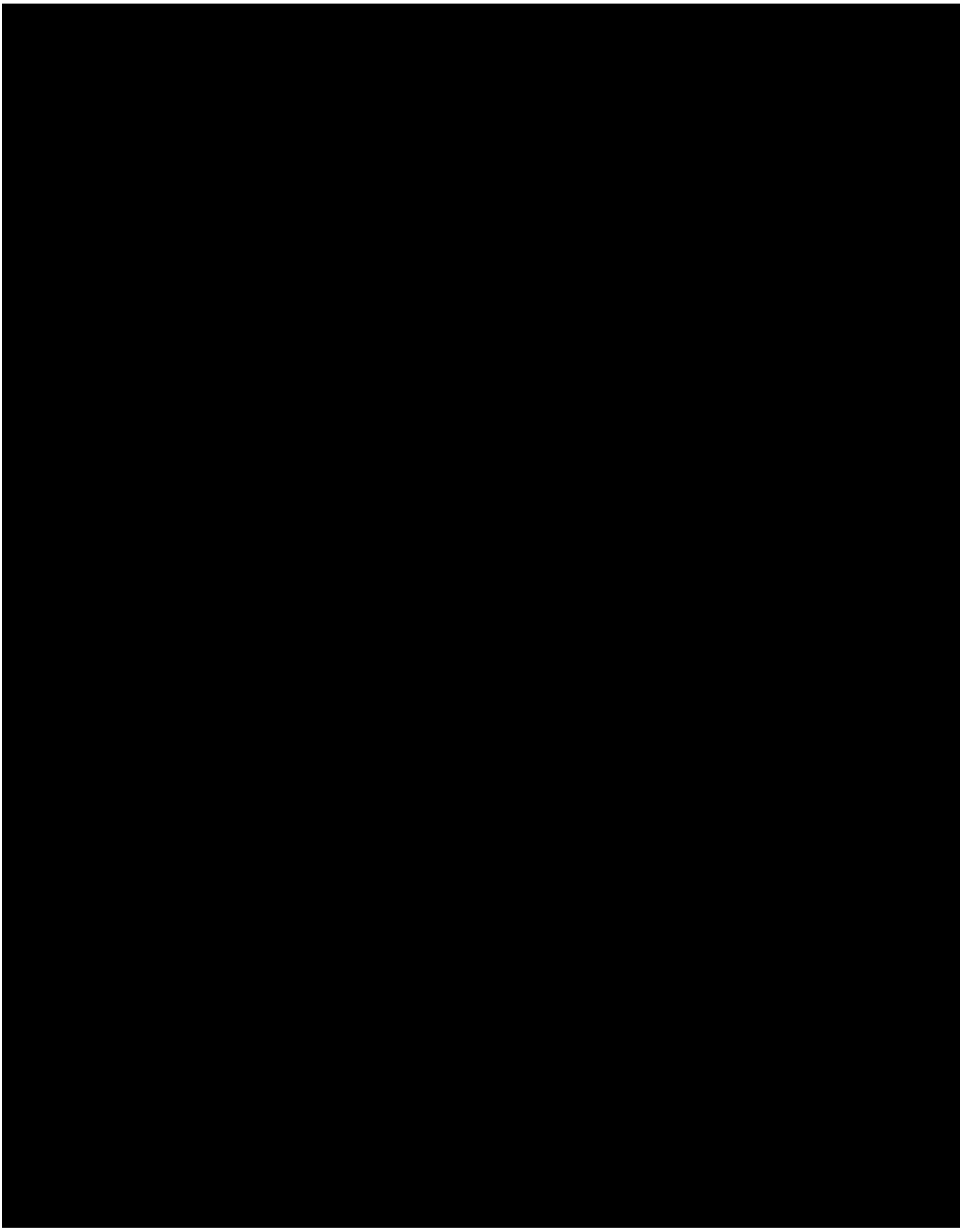
   1. Frequency Rarely All the time

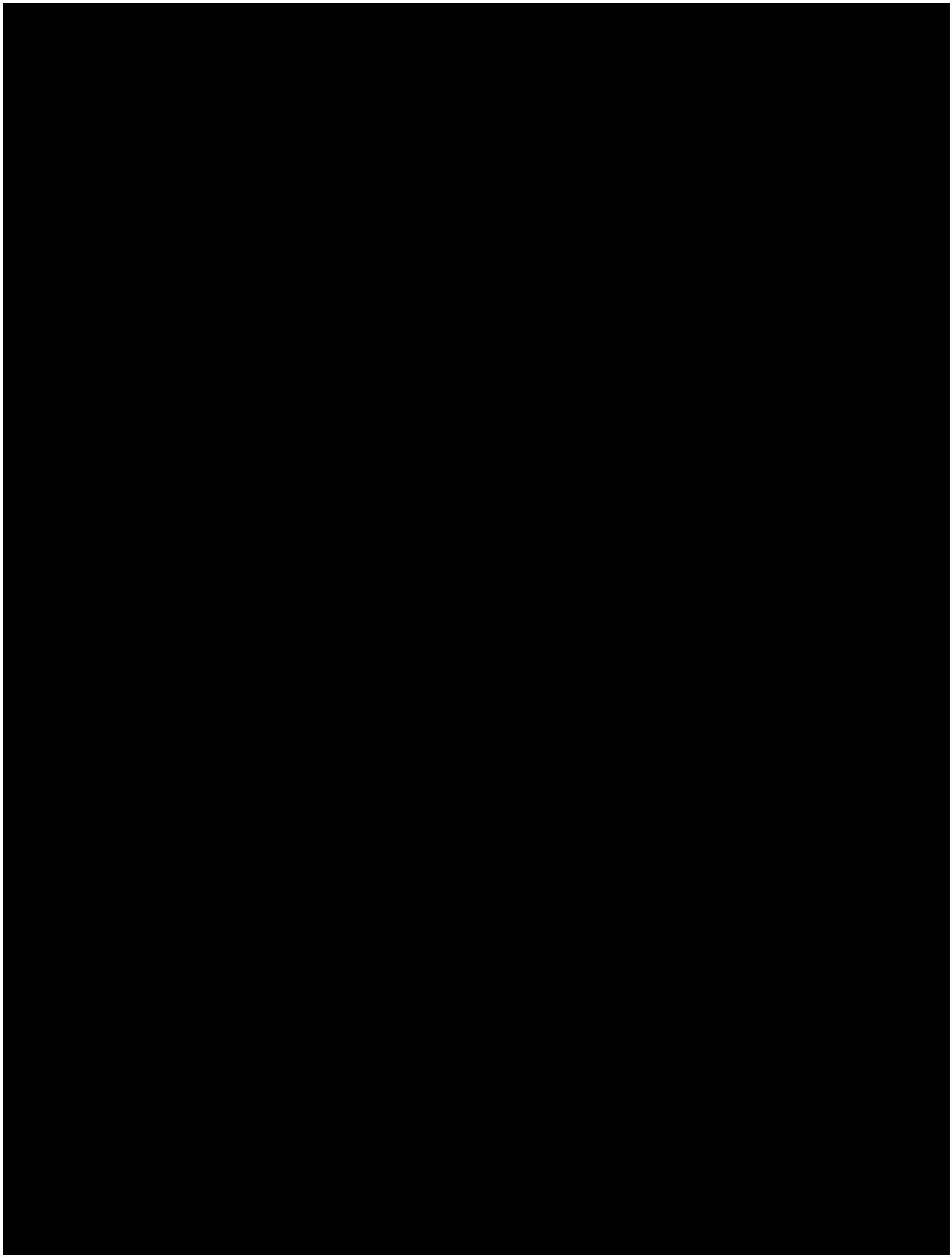
2. **Severity of symptoms:**

   Place a single vertical mark on the horizontal line to indicate how severe, on average, you feel your symptoms of dryness and/or irritation.

   2. Severity Very Mild Very Severe

[redacted]





[redacted]

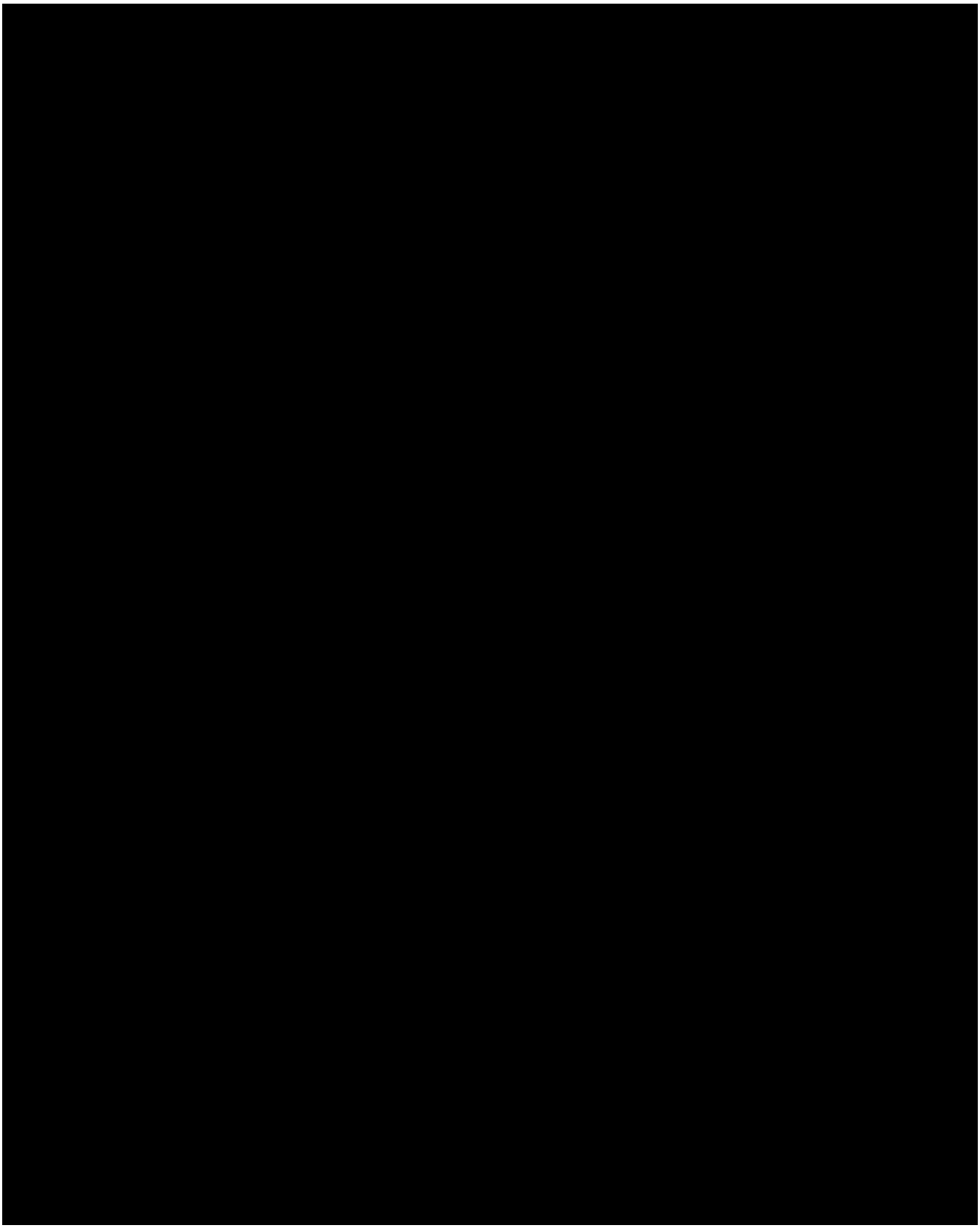
6.6.7 Unanesthetized Schirmer Test

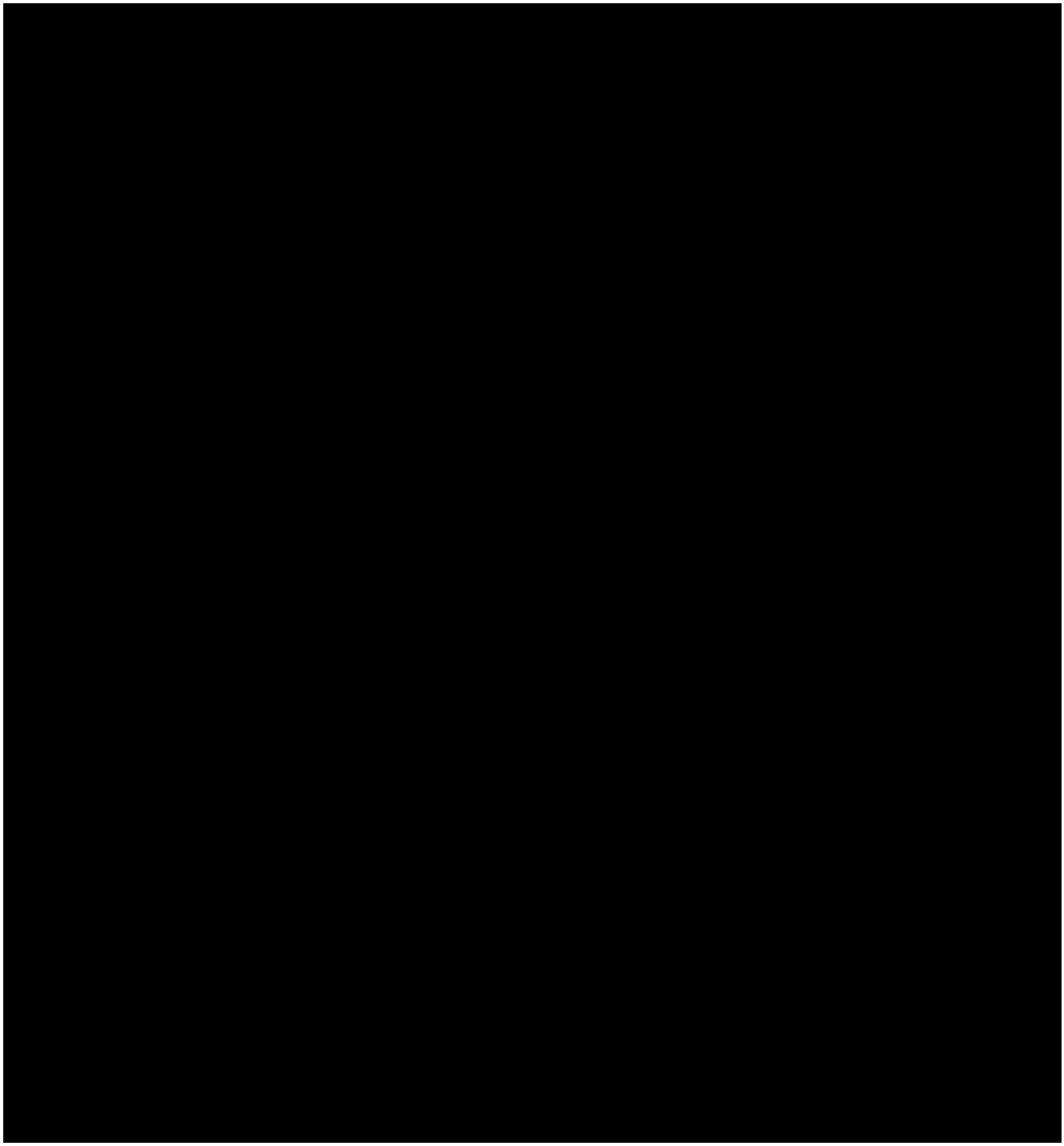
Two unanesthetized Schirmer tests will be performed on both eyes at each of the Baseline (Day 1), Day 7, Day 14, Day 28 and Day 90 visits.

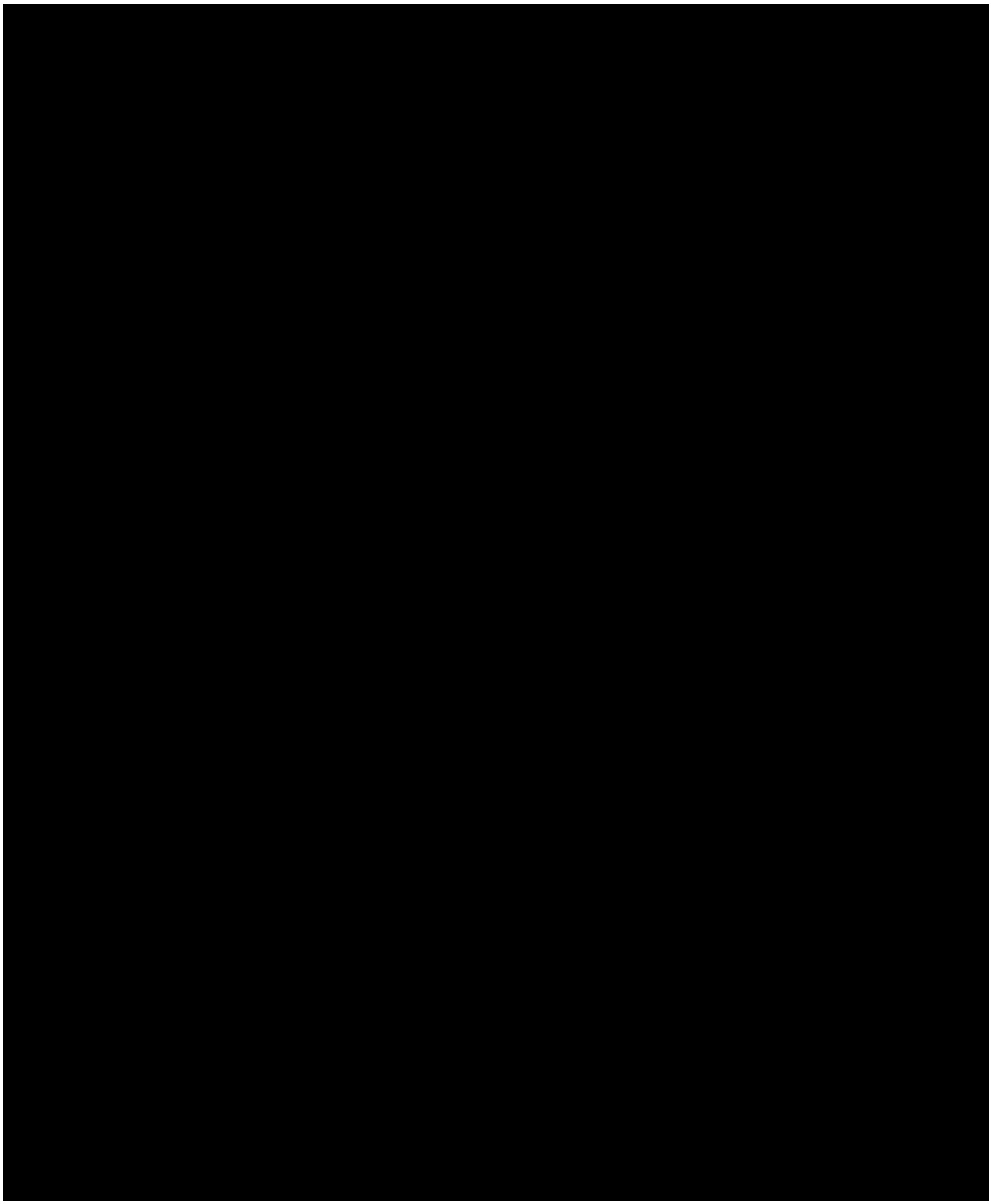
Placement and removal of the strips should be performed by the Investigator, sub-Investigator or designated trained personnel. Reading of the strips post-test, should be performed by only the Investigator or sub-Investigator. Every effort should be made to ensure the same individual(s) performs this assessment for a given subject at each applicable visit.

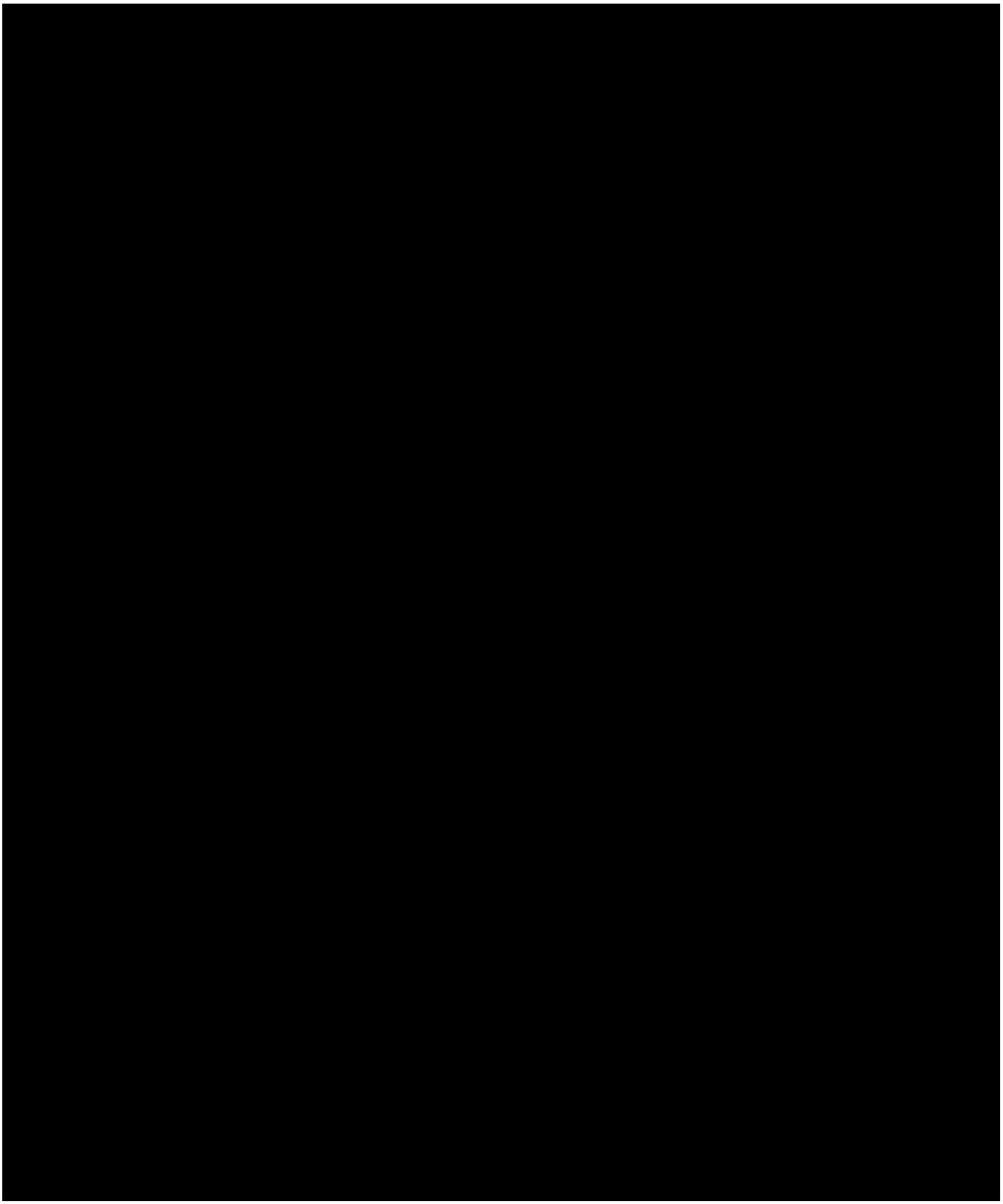
Additional details can be found in the Manual of Procedures.

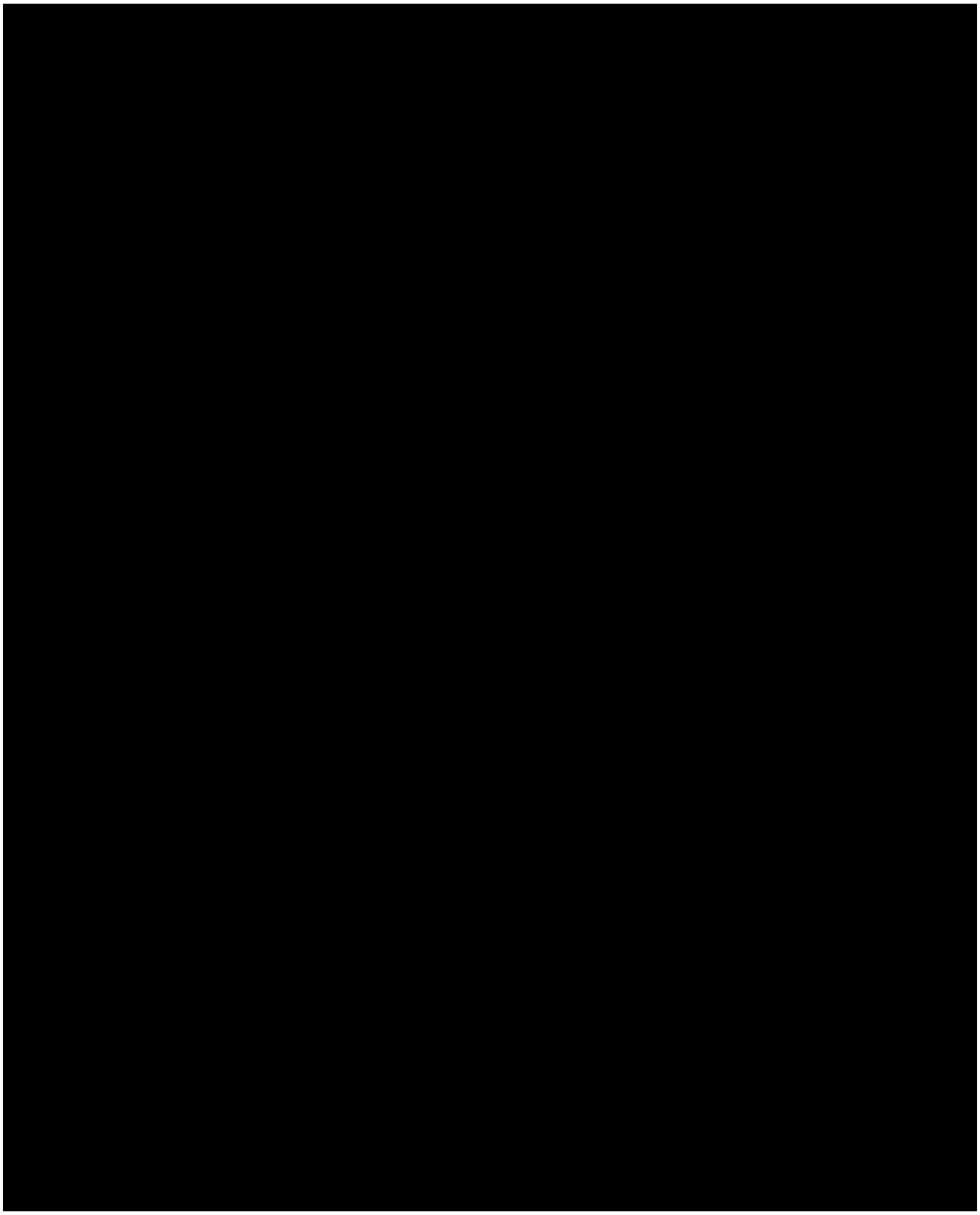
[redacted]











[redacted]

6.7.2 Controlled Adverse Environment Exposure

Subjects will be exposed to the CAE for approximately 90 minutes during the Screening visit. [redacted]

[redacted]

6.8 Safety Assessments

6.8.1 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 beats per minute.

6.8.2 Corrected Visual Acuity

Logarithmic minimum angle of resolution (LogMAR) visual acuity in both eyes must be assessed 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.

6.8.3 Biomicroscopy

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

- Cornea
- Conjunctiva
- Anterior Chamber

- Iris
- Lens
- Eyelid

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

6.8.4 Intraocular Pressure

The IOP must be measured in both eyes only after the biomicroscopic exam is completed and must be measured prior to pupil dilation. IOP will be taken by qualified study site personnel with the subject seated. Every effort should be made to ensure that the same study site personnel use 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.

6.8.5 Dilated Fundoscopy

Dilated fundus exams will be performed in both eyes 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 not clinically significant will be described. An indirect Fundoscopy 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.

6.9 Adverse Events Assessments

6.9.1 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

6.9.2 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 6.9.5.

- 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 (with no increase in severity).

- Unexpected AE or unexpected AR: an AE or AR is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. See Section 6.9.6.

6.9.3 Reporting Adverse Events

AEs should be documented from the time the subject provides informed consent until subject participation in the study has been completed. If a serious or non-serious AE or adverse reaction is unresolved at the time of exit, efforts will be made to follow up until the AE or adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event. These follow-up visits will be documented.

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

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

6.9.3.1 AEs and Prior Medical History

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

Symptoms and signs that are consistent with the natural history of DED are not considered reportable adverse events. Such developments are recorded but are not reportable adverse events. Worsening of symptoms and signs of DED should be recorded as an AE or SAE only if judged by the investigator to have unexpectedly worsened in severity and/or frequency or

changed in nature at any time during the study. When recording an unanticipated worsening of DED, it is important to convey why the development was unexpected.

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

6.9.4 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 6.9.8 for further information on SAEs, SARs, and suspected unexpected serious adverse reactions [SUSARs]).

6.9.5 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.

6.9.6 Expectedness

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

  For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or ARs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

- An Investigator must immediately (i.e., within 24 hours from time of awareness) report any SAE or SAR (see Section 6.9.2 for definitions) to the Sponsor or its clinical research organization (CRO) representative, whether or not considered drug-related, including those listed in the protocol or Investigator's Brochure.

6.9.7 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 Screening values will be documented as AEs.

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

6.9.8.1 Reporting SAEs or SARs

An Investigator must immediately (i.e., within 24 hours) report any SAE or SAR (see Section 6.9.2 for definitions) to the Sponsor or its CRO representative, whether or not considered study intervention-related, including those listed in the protocol or Investigator's Brochure. The Investigator must use the SAE report form and include an assessment of whether there is a reasonable possibility that the drug caused the event. The Investigator must report any SAE or SAR that occurs or is observed during the study. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form. The email or fax to submit the SAE report is found in Section 6.9.8.3.

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.

6.9.8.2 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.

6.9.8.3 SAE Report Contact Information

[redacted]

[redacted]

6.10 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
- Does not meet entry criteria
- Other

6.10.1 Actions after Discontinuation

Also see Early Termination Procedures (Section 7.3).

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 Early Termination Visit.

6.10.2 Discontinuation of the Entire Study

The entire study may be discontinued at any given site by the Investigator or the Sponsor or 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.

6.10.3 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 Screening and Run-In Period

7.1.1 Screening Visit (Day -14 [+3* days])

- Informed consent
- Demographics
- Medical, ophthalmic, and surgical history

- Prior or concomitant medication review
- Vital signs (heart rate and blood pressure)
- Urine pregnancy test (WOCBP only)
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness [redacted])
- SANDE Questionnaire (VAS)
- Corrected visual acuity
- Slit-lamp biomicroscopy
- At least 5-minute rest period

[redacted]

- CAE exposure

[redacted]

- Inclusion and exclusion criteriaAE Review
- Dispensing of the study intervention
- In office administration of study intervention by subject under site staff supervision
- Intraocular pressure
- Dilated fundus exam

* The Baseline visit is requested to be scheduled between 11 and 14 days after the Screening visit. If absolutely necessary, the Baseline visit may be delayed up to 7 days (extending the run-in period to a maximum of 21 days).

7.2 Randomized Intervention Period

7.2.1 Baseline (Day 1) Procedures

- Collection of used and unused study intervention
- Concomitant medication review
- AE review
- Vital signs (heart rate and blood pressure)
- Urine pregnancy test (WOCBP only)
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness [redacted])
- SANDE Questionnaire (VAS)

[redacted]

- Corrected visual acuity
- Slit-lamp biomicroscopy

[redacted]

- Inclusion and exclusion criteria review

- Randomization
- Dispensing of study intervention
- At least 30 and up to 45-minute rest period
- Pre-drop unanesthetized Schirmer test
- At least 15 and up to 20-minute rest period
- In office administration of study intervention by site staff
- Post-drop unanesthetized Schirmer test
- Hematology, chemistry, and urinalysis
- Intraocular pressure
- Dilated fundus exam

7.2.2 Day 7 (± 2 days) Procedures

- Concomitant medication review
- AE review
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness[redacted])
- SANDE Questionnaire (VAS)

[redacted]

- Corrected visual acuity
- Slit-lamp biomicroscopy

[redacted]

[redacted]

- Pre-drop unanesthetized Schirmer test
- At least 15 and up to 20-minute rest period
- In office administration of study intervention by site staff
- Post-drop unanesthetized Schirmer test

7.2.3 Day 14 (± 2 days) Procedures

- Collection of used and unused study intervention
- Concomitant medication review
- AE review
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness [redacted])
- SANDE Questionnaire (VAS)

[redacted]

- Corrected visual acuity
- Slit-lamp biomicroscopy

[redacted]

- Dispensing of study intervention
- At least 30 and up to 45-minute rest period

- Pre-drop unanesthetized Schirmer test
- At least 15 and up to 20-minute rest period
- In office administration of study intervention by site staff
- Post-drop unanesthetized Schirmer test

7.2.4 Day 28 (± 2 days) Procedures

- Collection of used and unused study intervention
- Concomitant medication review
- AE review
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness [redacted]
- SANDE Questionnaire (VAS)

[redacted]

- Corrected visual acuity
- Slit-lamp biomicroscopy

[redacted]

- Dispensing of study intervention
- At least 30 and up to 45-minute rest period
- Pre-drop unanesthetized Schirmer test
- At least 15 and up to 20-minute rest period

- In office administration of study intervention by site staff
- Post-drop unanesthetized Schirmer

7.2.5 Day 60 (± 5 days) Procedures

- Collection of used and unused study intervention
- Dispensing of study intervention

7.2.6 Day 90 (-2 / +5 days) Procedures

- Collection of used and unused study intervention
- Concomitant medication review
- AE review
- Vital signs (heart rate and blood pressure)
- Urine Pregnancy test (WOCBP only)
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness [redacted]
- SANDE Questionnaire (VAS)

[redacted]

- Corrected visual acuity
- Slit-lamp biomicroscopy

[redacted]

[redacted]

- Pre-drop unanesthetized Schirmer test
- At least 15 and up to 20-minute rest period
- In office administration of study intervention by site staff
- Post-drop unanesthetized Schirmer test
- Hematology, chemistry, and urinalysis
- Intraocular pressure
- Dilated fundus exam
- Study Exit

7.3 Early Termination Procedures

Every effort should be made to perform the following procedures at the Early Termination visit.

- Collection of used and unused study intervention
- Concomitant medication review
- AE review
- Vital signs (heart rate and blood pressure)
- Urine pregnancy test (WOCBP only)
- Corrected visual acuity
- Slit-lamp biomicroscopy
- Hematology, chemistry, and urinalysis
- Intraocular Pressure
- Dilated Fundus Exam
- Study Exit

7.4 Unscheduled Visits

An unscheduled visit may be any visit to the Investigator other than the visits specified in the protocol as possibly required for the subject's ophthalmic condition.

The investigator will perform all procedures necessary to evaluate the study participant at these visits and record any AEs in the eCRF.

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

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

All summaries will be presented by treatment group.

For the purpose of summarization, medical history, concurrent medications, 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 defined in the SAP.

Change from Baseline (CFB) will be calculated as post-Baseline result – Baseline; treatment comparisons will be calculated as AR-15512 – vehicle.

All primary and secondary analyses will be two-sided at a significance level of 0.05.

9.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints assessed at the eye level, the unit of analysis will be the "study eye" as defined in Section 9.3. For efficacy endpoints assessed OU, the unit of analysis with be the subject.

9.3 Study Eye Selection

The study subject must have at least one eye (the same eye) meeting all the inclusion criteria (Section 4.2) and none of the exclusion criteria (Section 4.3) at both Screening and Baseline visits where applicable. Study subjects will be dosed in both eyes. If both eyes are eligible at the time of randomization, the study eye will be defined as the eye with the lower pre-drop unanesthetized Schirmer score to be performed at the Baseline visit. If both eyes still qualify and have the same pre-drop unanesthetized Schirmer score, the right eye will be designated as the study eye

9.4 Missing Data

The primary analysis will be completed with available data per subject as specified in Estimand 1 from the intent-to-treat (ITT) population, assuming the overall study discontinuation rate is <5% in each arm. If the study discontinuation rate is ≥ 5% in each arm then the primary analysis will be based on multiple imputation methodology as specified in Estimand 2, and the available data analyses will become robustness analyses.

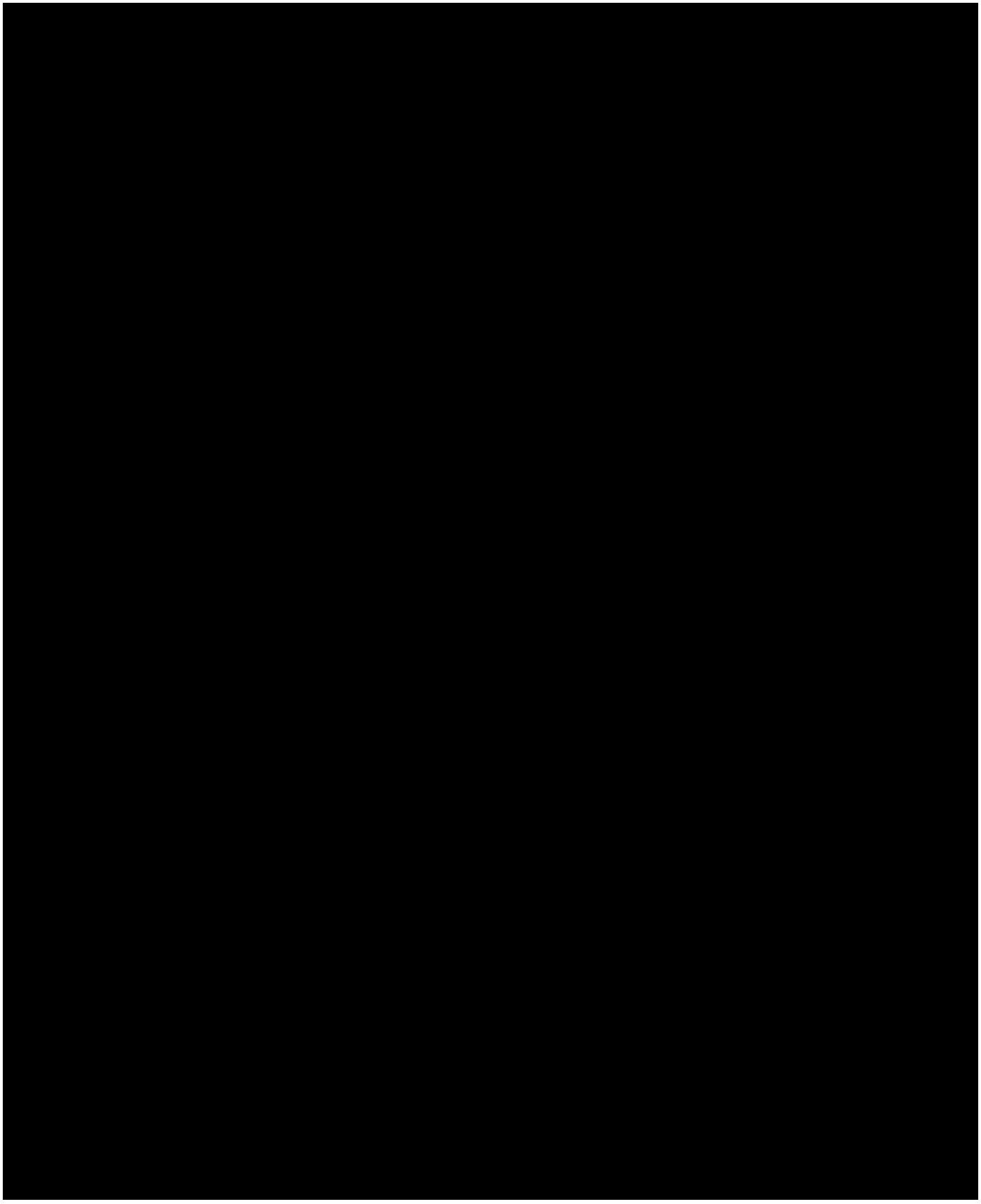
Additional robustness analyses will include repeating the primary analysis on the ITT population imputing missing data as failures for the proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14 endpoint; using multiple imputation methodology under different assumptions of missingness (at random and not at random) each using 30 imputed values; the ITT population imputing missing data using last observation carried forward (LOCF); the ITT population using trimmed means; and the per-protocol (PP) population with available data per subject.

9.5 Hypotheses

The primary endpoints will be tested as follows:

H_{01}: The difference between study eyes treated with AR-15512 (0.003%) and study eyes treated with vehicle, in the proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14 = 0.

H_{11}: The difference between study eyes treated with AR-15512 (0.003%) and study eyes treated with vehicle, in the proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14 ≠ 0.



[redacted]

9.7 Determination of Sample Size

Two hundred two (202) ITT population subjects (study eyes) per treatment group yields 99% power to conclude superiority of 0.003% AR-15512 over vehicle in the proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14, assuming a true difference of proportions (AR-15512 vs vehicle) of 80% vs 30% and a two-sided alpha = 0.05.

Additionally, 202 ITT population subjects (study eyes) per treatment group yields 99% power to conclude superiority of 0.003% AR-15512 over vehicle in the mean change from Baseline in SANDE score on Day 28 assuming a true difference (AR-15512 minus vehicle) of -7.9, a common SD of 17.72, and a two-sided alpha = 0.05.

Accounting for subject discontinuations, approximately 460 total subjects (230 per treatment arm) will be randomized assuming a dropout rate of 10%.

9.8 Analysis Populations

The following analysis population will be considered.

9.8.1 Intent-to-Treat Population

The intent-to-treat (ITT) population includes all randomized subjects. The primary efficacy analysis will be performed on the ITT population. Subjects in the ITT will be analyzed as randomized.

9.8.2 Per Protocol Population

The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations likely to seriously affect the primary outcome of the study and who complete the trial through Day 90. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.

9.8.3 Safety Population

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

9.9 Demographics and Baseline Characteristics

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

9.10 Efficacy Analyses

9.10.1 Primary Efficacy Endpoints

- Proportion of subjects ≥ 10 mm increase in unanesthetized Schirmer score on Day 14

9.10.2 Primary Efficacy Analyses

The primary comparison in this trial will be between AR-15512 (0.003%) and vehicle in the ITT population with available data per subject using Estimand 1 below if the overall study discontinuation rate is < 5%. If the discontinuation rate is ≥ 5%, this analysis will be a sensitivity analysis.

Estimand 1:

- Population: subjects in the ITT population with DED defined through enrollment criteria
- Endpoint:
    - Proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14
- Intercurrent event:
    - Discontinuation of investigational products is ignored. [treatment policy strategy]
    - Non-optimal compliance is ignored. [treatment policy strategy]
    - Withdrawal due to any reason. Missing data not imputed. [hypothetical strategy]
- Population-level summary:
    - Difference in the proportion of subjects ≥ 10 mm increase in unanesthetized Schirmer score on Day 14 between AR-15512 (0.003%) and vehicle

If the overall study discontinuation rate is ≥ 5% in each arm then the primary analysis will be based on multiple imputation methodology using Estimand 2 below. If the discontinuation rate is < 5% in each arm, this analysis will be a sensitivity analysis.

[redacted]

9.10.3 Secondary Efficacy Endpoints

- Change from Baseline in SANDE score on Day 28
- Change from Baseline in unanesthetized Schirmer score on Day 14

[redacted]

- Change from Baseline in SANDE Score on Day 90
- Change from Baseline in ODS - VAS on Day 90
- Change from Baseline in Eye Dryness - VAS Day 90

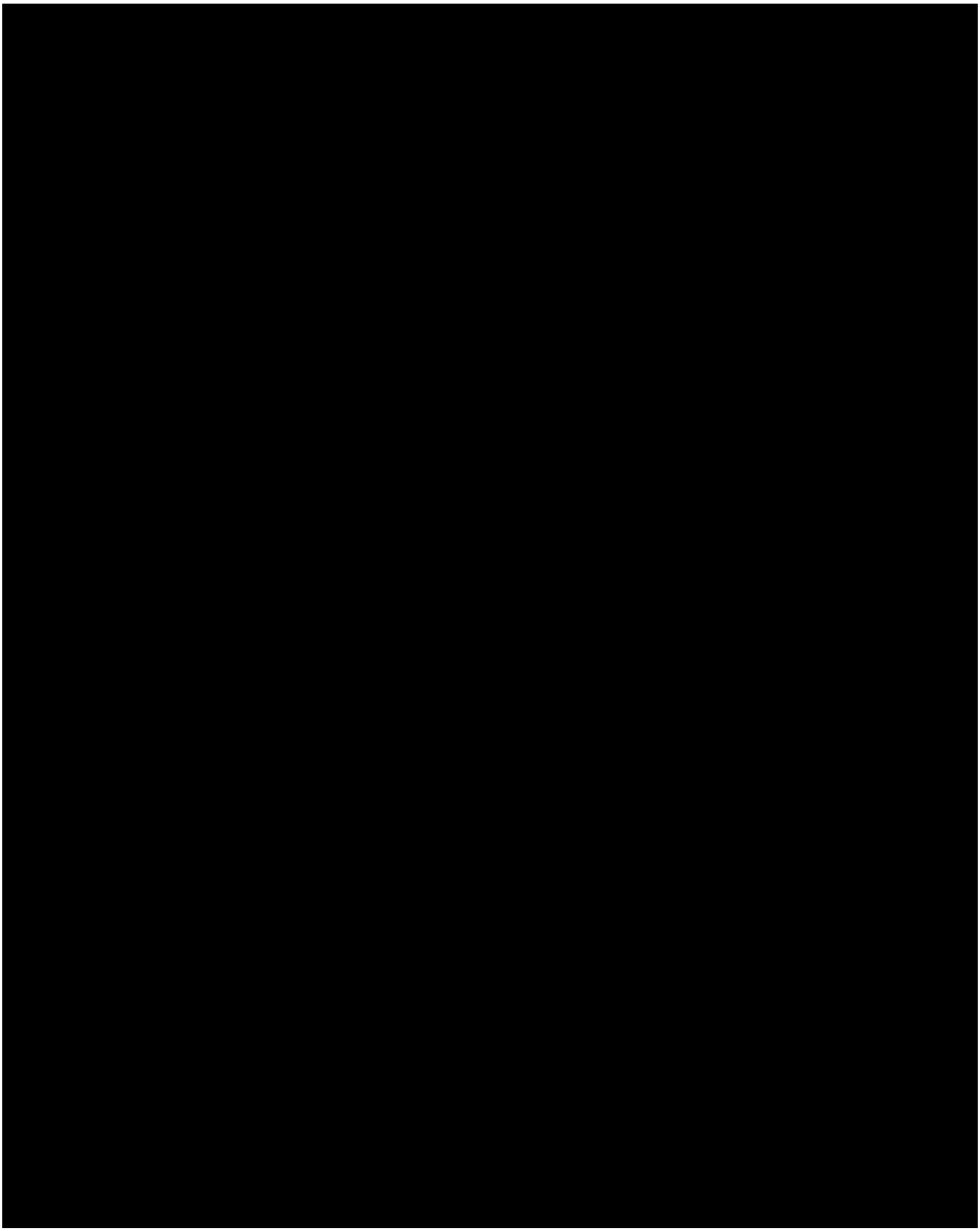
[redacted]

- Proportion of subjects ≥ 10 mm increase in unanesthetized Schirmer score on Day 90
- Change from Baseline in unanesthetized Schirmer score on Day 90

[redacted]

9.10.4 Secondary Efficacy Analyses

The secondary efficacy analyses will be conducted in the ITT population with intercurrent events handled as described in the missing data section. Changes from Baseline will be summarized by treatment group using continuous summary statistics and analyzed using an ANCOVA model with terms for Baseline value, treatment, and site. In addition, the study site by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across study sites. Least squares mean for each treatment group and for the difference between treatment groups will be presented from the model together with two-sided p-values and 95% confidence intervals. [redacted]



9.11 Safety Endpoints and Analyses

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages of treatment-emergent adverse events will be summarized at the subject level by system organ class and preferred term for all TEAEs, treatment related TEAEs, serious TEAEs, and TEAEs causing premature discontinuation of study drug by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of trial treatment. Similar summaries will be presented for all TEAEs by maximal severity. Separate summaries will be performed for ocular and non-ocular TEAEs.

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

In addition, changes from Baseline to worst on-treatment value for ocular safety assessments will be summarized.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators

The Principal Investigator 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 Approval

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, Title 21
- International Conference on Harmonization (ICH) Consolidated Good Clinical Practice Guideline (E6 R2)
- 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, and primary efficacy 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. Interactive response technology activities will be performed as described in the IRT User Manual.

10.9 Case Report Forms and Study Records

An investigator is 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 study intervention 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 case report forms (eCRFs). Each authorized study staff member will receive a unique access account in order to use the Electronic Data Capture (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 and medical license, completed FDA Form 1572 / Statement of Investigator, each eCRF, subject charts/source documents, Investigator's Brochure, Investigator's Brochure amendments, protocol, protocol amendments, correspondence with the Sponsor and the IRB, IP 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 Practice [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 regulatory authority as a serious breach of GCP and the protocol. If per the relevant regulatory 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, designate, and/or approve 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 (DHHS), and other domestic government 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 SAP.

10.13 Retention of Data

The Investigator's site and clinical laboratory will retain all records related to the study in compliance with ICH GCP 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 Procedures

	Start of 2 Week Run-In (AR-15512 Vehicle)	Randomized Study Intervention Period (BID-OU, 1:1 Randomization 0.003% AR-15512: AR-15512 Vehicle)						
Visit[1]	**Screening (Day -14)**	**Baseline (Day 1)**	**Day 7**	**Day 14**	**Day 28**	**Day 60**	**Day 90 (Study Exit)**	**Early Termination**
Visit Window (Days)	+3[2]	N/A	±2	±2	±2	±5	-2/+5	N/A
Informed consent	X							
Demographics	X							
Collection of used / unused study intervention		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	X	X	X	X	X		X	X
Vital signs (heart rate and blood pressure)	X	X					X	X
Urine pregnancy test (WOCBP only)	X	X					X	X
Symptom questionnaire (VAS) (Ocular Discomfort, Eye Dryness [redacted])	X	X	X	X	X		X	
SANDE questionnaire (VAS)	X	X	X	X	X		X	
[redacted]								
Corrected visual acuity	X	X	X	X	X		X	X
Slit-lamp biomicroscopy	X	X	X	X	X		X	X
[redacted]								

	Start of 2 Week Run-In (AR-15512 Vehicle)	Randomized Study Intervention Period (BID-OU, 1:1 Randomization 0.003% AR-15512: AR-15512 Vehicle)						
Visit[1]	**Screening (Day -14)**	**Baseline (Day 1)**	**Day 7**	**Day 14**	**Day 28**	**Day 60**[6]	**Day 90 (Study Exit)**	**Early Termination**
At least 10-minute rest period	X	X	X	X	X		X	
[redacted]								
CAE exposure	X							
[redacted]								
Inclusion and exclusion criteria	X	X						
Randomization		X						
Dispensing of study intervention[4]	X	X		X	X	X		
At least 30 and up to 45-minute rest period		X	X	X	X		X	
Pre-drop unanesthetized Schirmer test		X	X	X	X		X	
At least 15 and up to 20-minute rest period		X	X	X	X		X	
In office administration of study intervention[5]	X	X	X	X	X		X	
Post-drop unanesthetized Schirmer test		X	X	X	X		X	
Hematology, chemistry, and urinalysis		X					X	X
Intraocular pressure	X	X					X	X
Dilated fundus exam	X	X					X	X
Study exit							X	X

1. All office visits must be arranged at approximately the same time of day ± 1 hour
2. The Baseline visit should be scheduled between 11 and 14 days after the Screening visit. If absolutely necessary, the Baseline visit may be delayed up to 7 days (extending the run-in period to a maximum of 21 days)
3. Administered every 5 minutes while in the CAE

4. Day 7 Randomized Intervention Kit is not to be dispensed home to the subject. A single vial is used at the Day 7 visit and then returned to the kit. The single used vial as well as remaining 4 unused vials are to be retained for accountability.
5. Study intervention must be removed from the refrigerator at least 30 minutes before use
6. Dispensing and collection visit only