Clinical Study Protocol

Study Title: A Phase 2b Study Evaluating the Safety and Efficacy of AR-15512 Ophthalmic Solution for the Treatment of Dry Eye Disease (COMET-1)

Study Number: AR-15512-CS201

Study Phase: 2b

Product Name: AR-15512 Ophthalmic Solution

Indication: Treatment of the signs and symptoms of dry eye disease

Investigators: Multicenter

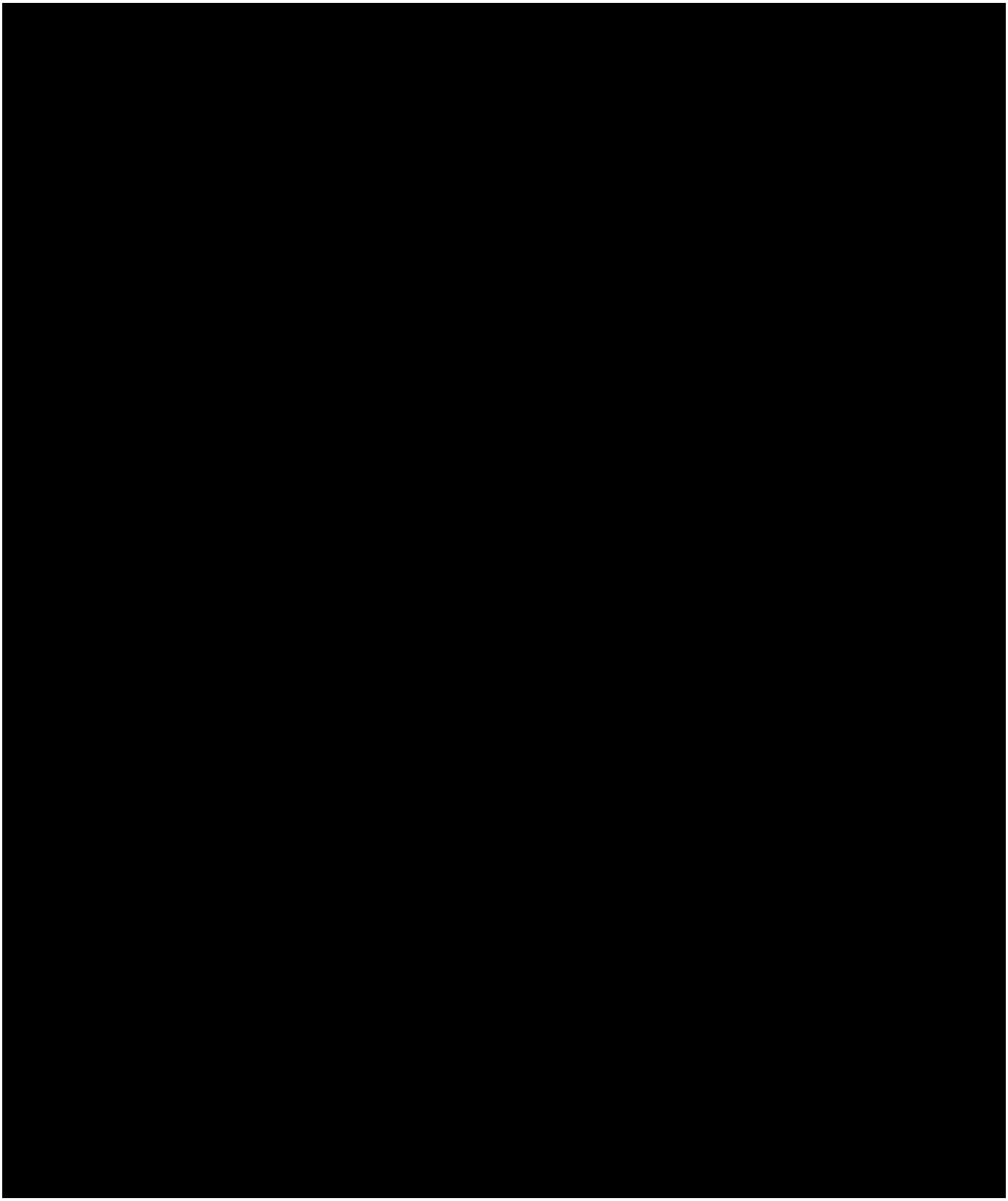
Sponsor: Aerie Pharmaceuticals, Inc.
550 Hills Drive, 3rd Floor
Bedminster, NJ 07921

[redacted]

NCT Number: 04498182

Original Protocol (Rev. 0):	06 August 2020
Amendment 1 (Rev. 1)	13 November 2020
Amendment 2 (Rev. 2)	11 January 2021
Amendment 3 (Rev. 3)	28 January 2021
Amendment 4 (Rev. 4)	02 April 2021

Confidentiality Statement



CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 2b Study Evaluating the Safety and Efficacy of AR-15512 Ophthalmic Solution for the Treatment of Dry Eye Disease

Study No: AR-15512-CS201

Original Protocol Date: 06 August 2020

Protocol Version No.: Rev. 4

Protocol Version Date: 02 April 2021

[redacted]

SYNOPSIS

Sponsor: Aerie Pharmaceuticals, Inc.
Name of Finished Product: AR-15512 ophthalmic solution 0.0014% or 0.003%
Name of Active Ingredients: AR-15512
Study Title: A Phase 2b Study Evaluating the Safety and Efficacy of AR-15512 for the Treatment of Dry Eye Disease
Study Number: AR-15512-CS201
Study Phase: 2b
Primary Objective(s): To evaluate the safety, tolerability and efficacy of 2 doses (0.0014% and 0.003%) of topical ophthalmic AR-15512 compared to its vehicle dosed twice daily (BID) in subjects with dry eye disease (DED).
Study Design: This will be a Phase 2b, multicenter, vehicle-controlled, double-masked, randomized study conducted at approximately 15 sites in the United States. All subjects enrolled will have DED. The study will consist of Screening and Baseline visits as well as follow-up visits at Day 14 (Visit 3), 28 (Visit 4) and 84 (Visit 5 / Study Exit). All subjects will be exposed to the Controlled Adverse Environment (CAE®) at the Screening, Baseline, Day 28 (at Selected Sites) and Day 84 visits. At the end of the Screening Visit, all qualified subjects will be assigned to administer AR-15512 vehicle BID to both eyes for 14 days (vehicle run-in period). After the vehicle run-in period, subjects will be re-evaluated 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 1:1:1 ratio within each site, to receive AR-15512 0.0014%, AR-15512 0.003% or AR-15512 vehicle to be administered BID as 1 drop in each eye for 84 days. Efficacy will be assessed at Visit 3 without use of the CAE and at Visits 4 and 5, pre-, during and post- use of the CAE. At the end of Visit 5, subjects will exit the study. Safety assessments will be conducted at each study visit. **Key Inclusion Criteria** Subjects must meet all of the following criteria to enter into the study: • Have used and/or desired to use artificial tears for DED symptoms within 2 months prior to the Screening visit
[redacted]

[redacted]

- Best-Corrected Visual Acuity (BCVA) 20/200 (+0.70 LogMAR) or better in both eyes at the Screening and Baseline visits

Key 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:

- History or presence of any ocular disorder or condition (other than DED) in either eye that would, in the opinion of the investigator, likely 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
- Use of contact lenses in either eye within 7 days prior to the Screening visit or planned use during the study
- Use of artificial tears within 2 hours prior to the Screening visit or anticipated use during the study
- Regular use of lid hygiene within 14 days prior to the Screening visit or any planned use during the study
- Regular use of any topical ocular medications (including use of ocular cyclosporine or other prescription ophthalmic solution for DED (e.g., Restasis®, Cequa™, Xiidra®), topical ocular corticosteroid- or non-steroidal-anti-inflammatory agents, glaucoma medications, eye whitening products (e.g., Visine®, Lumify®), topical antibiotics, antihistamines, mast cell stabilizers, or other over-the-counter [OTC], herbal, prescription, or nutritional supplements with the exception of artificial tears), within 30 days prior to the Screening visit or anticipated use during the study. Note: Occasional (as needed) use > 24 hours prior to the Screening Visit may be permitted
- Use of medications associated with 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 90 days prior to the Baseline Visit or anticipated use during the study
- Use of systemic immunomodulators (e.g., hydroxychloroquine, methotrexate, cyclosporine) started < 90 days prior to the Baseline Visit or a change in dosage is anticipated during the study
- Use of systemic corticosteroids started < 90 days prior to the Baseline Visit or a change in dosage is anticipated during the study. Note: Non-ocular topically applied corticosteroids (including nasal sprays and inhalers) will be permitted during the study and the dose is not required to be stable
- Any systemic medication known to cause ocular drying (e.g., antihistamines, antidepressants, beta-blockers) started < 14 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Occasional (as needed) use of medications such as systemic antihistamines will be permitted
- Use of TrueTear® within 45 days of the Screening visit
- Use of lid heating therapy (i.e., LipiFlow®, iLUX®) or Meibomian gland probing/therapeutic expression within 1 year prior to the Screening visit

Study Population:

This study is anticipated to enroll approximately 360 subjects with DED so as approximately 324 subjects complete Day 84. The anticipated drop out rate is 10%. To achieve this goal, approximately 1500 subjects may be screened.

Investigational Product, Dose, and Mode of Administration:

BID topical ocular administration of AR-15512 ophthalmic solution 0.0014%, AR-15512 ophthalmic solution 0.003% or AR-15512 vehicle

Duration of Treatment:

Approximately 14 weeks of BID dosing of 1 drop to each of both eyes

Efficacy Assessments:

Primary Assessments:

- Ocular Discomfort Score (ODS) based on Visual Analog Scale (VAS)
- Anesthetized Schirmer test

Secondary Assessments:

- Ocular Pain Score based on VAS
- SANDE (Symptom Assessment iN Dry Eye) Questionnaire Score
- Eye Dryness Score based on VAS

[redacted]

Safety Assessments:

- Adverse events
- Hematology, chemistry, and urinalysis
- Best-corrected visual acuity
- Intraocular pressure
- Dilated fundus exam

Statistical Methods:

Sample Size Determination

One hundred and eight (108) ITT population subjects (study eyes) per treatment group yields 90% power to conclude superiority of AR-15512 (0.003% or 0.0014%) over vehicle in the mean change from baseline (CFB) pre-CAE ODS-VAS at Day 28, assuming a true difference (AR-15512 minus vehicle) of -8.5, a common standard deviation of 19.0, and a two-sided alpha = 0.05.

Additionally, 108 ITT population subjects (study eyes) per treatment group yields 90% power to conclude superiority of AR-15512 (0.003% or 0.0014%) over vehicle in the mean CFB in pre-CAE anesthetized Schirmer score at Day 28 assuming a true difference (AR-15512 minus vehicle) of 1.4 mm, a common standard deviation of 3.15 mm, and a two-sided alpha = 0.05.

Accounting for subject discontinuations, approximately 360 total subjects (120 per treatment arm) will be randomized assuming a dropout rate of 10%.

Analyses

The co-primary efficacy endpoints will be: • Change from baseline in pre-CAE ODS-VAS at Day 28 • Change from baseline in pre-CAE anesthetized Schirmer score at Day 28
Date of Original Approved Protocol (Rev. 0): 06 August 2020
Date of Most Recent Protocol Amendment 4 (Rev. 4): 02 April 2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BCVA	Best-Corrected Visual Acuity
BID	Twice Daily
CAE	Controlled Adverse Environment
CDVA	Corrected Distance Visual Acuity
CFB	Change From Baseline
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DED	Dry Eye Disease
EDS	Eye Dryness Score
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat

IV	Intravenous
IWRS	Interactive Web Response System
LFU	Lacrimal Functional Unit
LOCF	Last Observation Carried Forward
[redacted]	
MGD	Meibomian Gland Disease
min	Minute
NEI	National Eye Institute
OCT	Optical Coherence Topography
ODS	Ocular Discomfort Score
OP	Ocular Pain
OTC	Over the Counter
PP	Per Protocol
SAE	Serious Adverse Event
SANDE	Symptoms Assessment iN Dry Eye
SAR	Suspected Adverse Reaction
SSAR	Serious Suspected Adverse Reaction
SUSAR	Serious Unexpected Adverse Reaction
[redacted]	
TID	Three times a day
[redacted]	
TRPM8	Transient Receptor Potential Melastatin 8
VAS	Visual Analogue Scale
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

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).

DED is a chronic condition with a multifactorial etiology (Bron 2017) and has been the focus of significant research for over 30 years. 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 more common in women, especially after menopause and its prevalence increases with age in both genders (Gayton 2009, Stapleton 2017). 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.

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).

It is now understood that the tear-secreting glands and the ocular surface form an integrated lacrimal functional unit (LFU) via sensory and autonomic nerves designed to maintain the health of the ocular surface. Dysfunction in any component of the LFU leads to tear instability and inflammation and the development of DED (Baudouin 2014, Bron 2017, Stern 2004).

Treatment of DED is mainly symptomatic and very few specific pharmacological 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 2 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. 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 (TRP) 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). TRPM8 knockout mice are characterized by dramatically reduced basal tearing and an abrogated cold responsiveness without any effect on nociceptor-mediated irritative tearing (Dhaka 2007). 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 TRPM8 receptor agonist. Aerie acquired AR-15512 from Avizorex, who began the development of AR-15512 ophthalmic solution. AR-15512 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 (FL-no. 16.123) is generally recognized as safe 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, *ex vivo* and *in vivo* nonclinical studies were conducted in order to characterize the pharmacological actions and to describe the safety and toxicity profile of AR-15512 and AR-15512 ophthalmic solutions. Primary pharmacodynamics studies were conducted in *in vitro* cell culture, *ex vivo* with isolated excised corneas (guinea pig), and *in vivo* (guinea pigs). These studies characterized the mechanism of action of AR-15512 and investigated the effective dose and the dosing regimen of ocular administration of AR-15512 ophthalmic solutions. Altogether these data 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 regulation of basal tear production and blink rate.

A series of nonclinical safety studies (non-GLP and GLP) were conducted demonstrating that AR-15512 is non-mutagenic, non-irritating, non-sensitizing, and non-phototoxic. AR-15512 ophthalmic solutions were well-tolerated locally after repeated topical ocular administration with negligible systemic (plasma) exposure. The lack of ocular and systemic toxicity, including toxicokinetics, was demonstrated after repeated administration in rats (IV), rabbits (ocular) and dogs (ocular). The lack of carcinogenicity, reproductive and developmental toxicity associated with AR-15512, is also supported by peer-reviewed literature and the

historical safe use of AR-15512 as a flavoring agent or adjuvant in or on human food products. Altogether, the safety, tolerability and wide therapeutic index of AR-15512 fully support this Phase 2b clinical study and overall clinical development program planned by Aerie.

To date, 1 clinical study with AR-15512 has been performed (AVX012-CT-001). This Phase 1/2a multi-center, randomized, double-masked study was conducted in Spain by Avizorex Pharma S.L. ("Avizorex"). The study was conducted in two parts to assess the safety of topical ocular administration of two concentrations (0.0007% and 0.0014%) of AR-15512 dosed three times daily (TID) for 7 days (Part A), followed by assessment of efficacy and safety of the concentration elevated from Part A dosed either twice daily (BID) or TID for 28 days consecutively in subjects with DED.

The concentration elevated to Part B of the study was 0.0014%. Topical ocular administration BID or TID of AR-15512 0.0014% for 28 consecutive days resulted in an improvement of DED symptoms and signs (tear production and tear stability).

AR-15512 was found to be safe and well tolerated throughout the entire study. In Part A of the study, a total of 4 adverse events (AEs) were reported in 4 subjects (16.7%). During Part B, a total of 68 AEs were reported in 43 subjects (39.4%). Of these, 19 AEs in 16 subjects were considered treatment-related, with eye pruritis the most common. Ten (9.2%) subjects discontinued from study treatment due to AEs (2 each on AR-15512 BID, vehicle BID and vehicle TID and 4 on AR-15512 TID). No serious AEs were reported during the study.

The majority of AEs reported in both Parts A and B were considered mild in severity with few cases considered moderate (9/72 [12.5%] moderate AE events in 47 subjects; of these, 4/72 [5.6%] were moderate ocular AEs coded to the SOC of Eye Disorders). No AEs were considered severe. No other clinical studies have been completed with AR-15512 ophthalmic solution.

The totality of data collected to date supports continued development of AR-15512 for the treatment of the signs and symptoms of DED. It should be noted that since the completion of the Phase 1/2a study, Aerie has modified the formulation slightly from that utilized by Avizorex by lowering the HPMC concentration from 0.45% to 0.14%. This Phase 2b clinical study will be conducted with this new formulation.

1.1 Summary of Findings from Nonclinical Studies with AR-15512

Detailed information on nonclinical studies with AR-15512 can be found in the Investigator's Brochure (IB) for AR-15512.

1.1.1 Product Overview

AR-15512 is the active pharmaceutical ingredient in AR-15512 ophthalmic solution 0.0014% or 0.003%. AR-15512 is a potent and selective agonist of Transient Receptor Potential Melastatin 8 (TRMP8) ion channel and a member of the menthyl amide class (Figure 1).

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. Altogether, the mechanism of action of AR-15512 may represent an effective treatment for the signs and symptoms of DED.

[redacted]

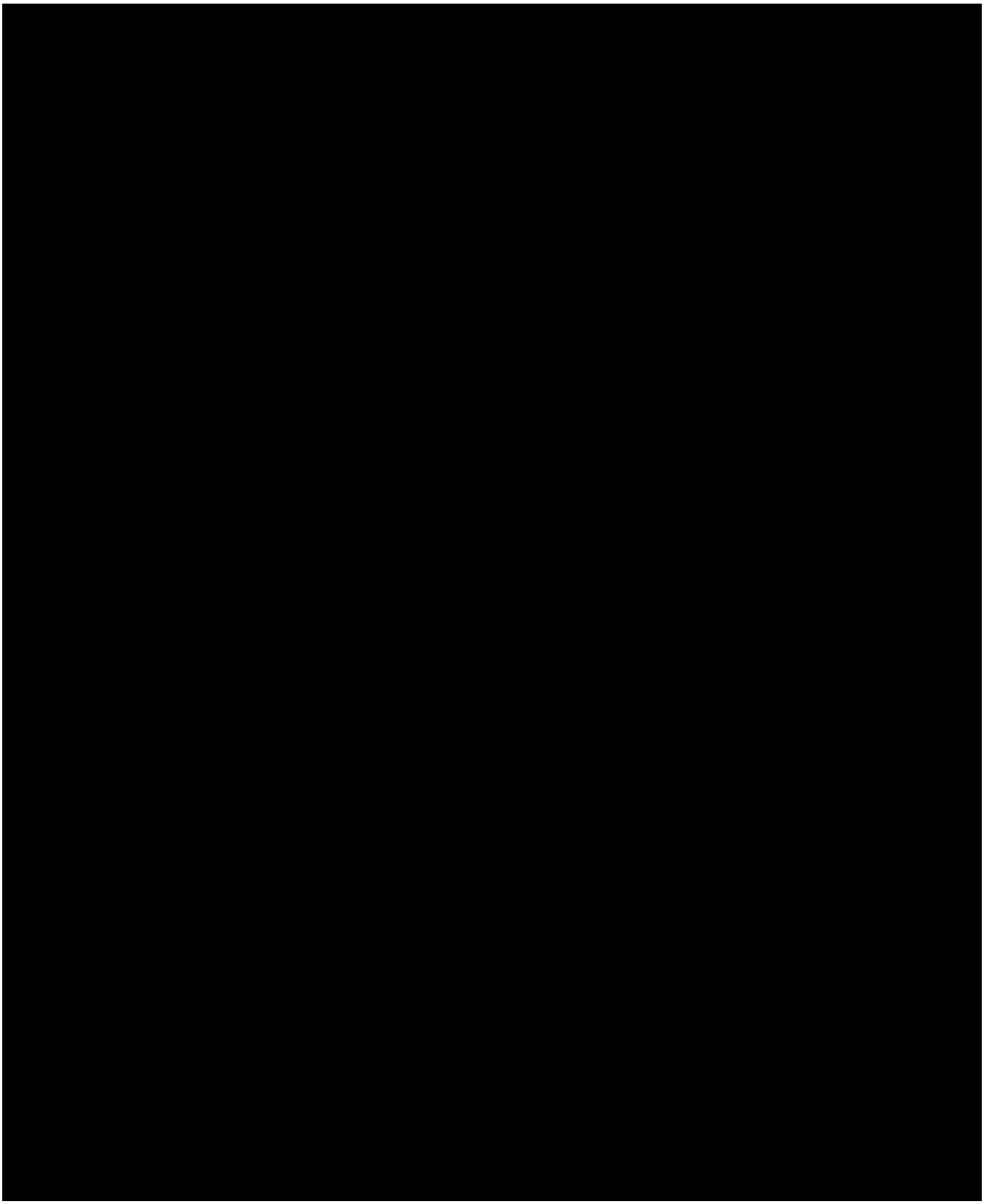
1.1.2 In Vitro/In Vivo Primary Pharmacology

Mechanistically, cold sensitive ocular thermoreceptors are believed to be linked to basal tearing based on their presence on sensory afferent neurons that play a role as "humidity detectors", enabling a response to gradual and subtle temperature decreases of the ocular surface caused by evaporation of the tear film during interblink periods (Belmonte 2017, Yang 2017, Yang 2018). Studies have shown that TRPM8 receptors have a key role in the maintenance of tear film homeostasis, for example, transgenic TRPM8 knockout mice have dramatically reduced basal tearing and an abrogated cold responsiveness without any effect on nociceptor-mediated irritative tearing (Dhaka 2007). AR-15512 has been shown to modulate ocular surface wetness through the activation of TRPM8 stimulating production of basal tearing (Abelson, 2013, Belmonte 2015).

To date, available data support the efficacy of AR-15512 as a specific agonist of TRPM8 channels of cold thermoreceptor sensory nerve fibers in the cornea, and activation (via AR-15512) of nerve impulse activity in these nerve fibers result in regulation of basal tear production and blink rate. This modulation of basal tear production and blink rate support AR-15512 efficacy as a novel treatment strategy for DED.

1.1.3 Nonclinical Toxicity

A series of non-GLP and GLP studies was conducted demonstrating that AR-15512 is non-cytotoxic, non-mutagenic, non-irritating, non-sensitizing, and non-phototoxic. AR-15512 ophthalmic solutions were well-tolerated locally and systemically after repeated topical ocular administration with negligible systemic (plasma) exposure (i.e., wide margin of safety). Ocular and systemic toxicity, including toxicokinetics, was assessed after repeated administration in rats (IV), rabbits (ocular) and dogs (ocular) up to 90 days. Additional nonclinical safety data, including carcinogenicity, and reproductive and developmental toxicity, is based upon historical safe use of AR-15512 as a flavoring agent or adjuvant in or on human food products (USFDA/FEEMA GRAS, EU/EFSA, WHO/JECFA) as well as peer-reviewed scientific literature and patient data as summarized in Section 1.2.2.



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1.2.3 Risks and Benefits to Human Subjects with AR-15512

To date, *in vitro* and *in vivo* nonclinical studies have been carried out in order to characterize the efficacy of AR-15512 as a specific agonist of TRPM8 channels of cold thermoreceptor sensory nerve fibers in the cornea and ability of AR-15512 to stimulate nerve impulse activity in these nerve fibers to result in regulation of tear production and blink rate.

In vitro, *in vivo* and *ex vivo* studies have also been performed 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 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 2b study.

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 several years. AR-15512 (FL-no. 16.123) is generally recognized as safe 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).

To date, 1 clinical study with AR-15512 has been performed. BID daily topical ocular administration of AR-15512 0.0014% for 28 days resulted in an improvement of DED symptoms and signs (tear production and tear stability). AR-15512 was found to be safe and well tolerated throughout the entire study. The majority of all AEs were considered mild in severity with few cases considered moderate and none considered severe. 19 AEs in 16 subjects were identified as treatment-related, with eye pruritis the most common.

DED is a chronic disease effecting approximately 5% to 50% of the global population ≥ 50 years old. DED results in changes to the tear film that 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. DED represents a significant health care burden, contributing to approximately 25% of visits to ophthalmic clinics 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.

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 1 (Xiidra®), is indicated for the treatment of the 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 both the design of this Phase 2b study and the rationale for continuing 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, tolerability and efficacy of 2 doses (0.0014% and 0.003%) of topical ophthalmic AR-15512 compared to its vehicle administered BID in subjects with DED.

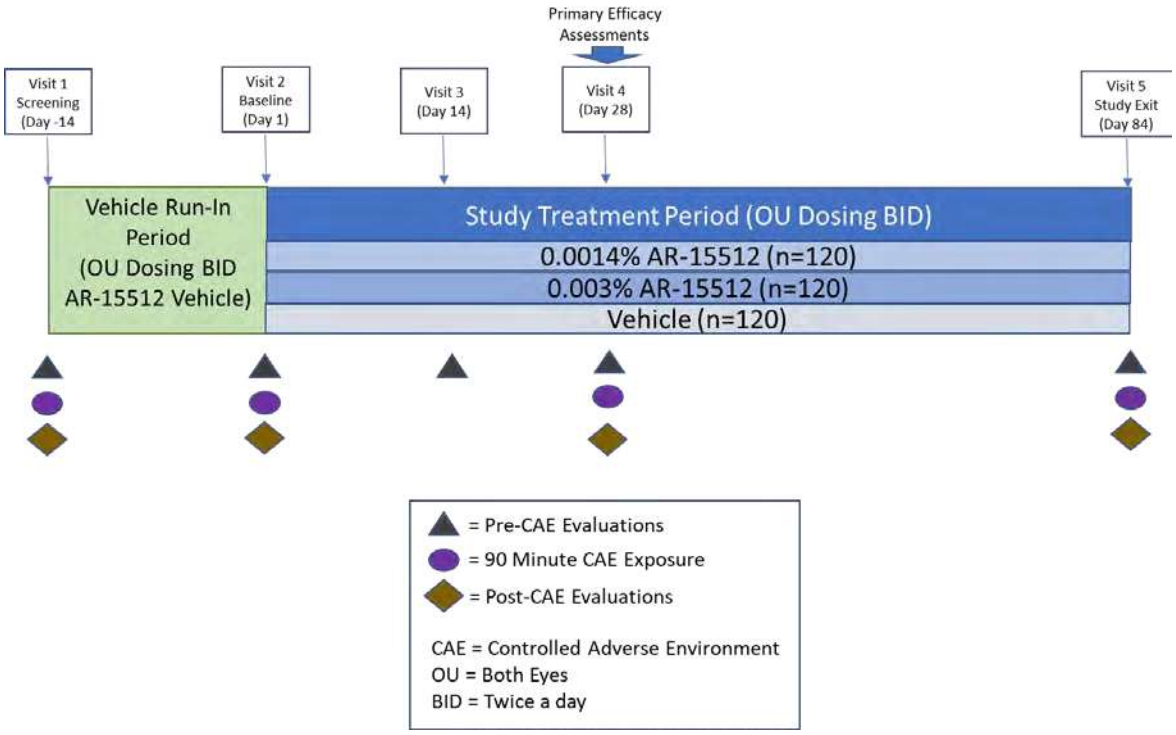
3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This will be a Phase 2b, multicenter, vehicle-controlled, double-masked, randomized study conducted at approximately 15 sites in the United States. All subjects enrolled will have DED. The study will consist of Screening and Baseline visits as well as follow-up visits at Day 14 (Visit 3), 28 (Visit 4) and 84 (Visit 5 / Study Exit). All subjects will be exposed to the CAE at the Screening, Baseline, Day 28 and Day 84 visits. A summary of the overall study design is found in Figure 2.

At the end of the Screening Visit, all qualified subjects will be assigned to administer study vehicle BID to both eyes for 14 days (vehicle run-in period). After the vehicle run-in period, subjects will be re-evaluated for signs and symptoms of DED. Only subjects who requalify, based on inclusion/exclusion criteria, will be enrolled in the study and randomized at a 1:1:1 ratio within each site, to receive AR-15512 0.0014%, AR-15512 0.003% or AR-15512 vehicle to be administered as 1 drop in each eye twice daily for 84 days. Efficacy will be assessed on Visit 3 without use of the CAE and at Visits 4 and 5 pre-, during and post- use of the CAE. Safety assessments will be conducted at each study visit. At the end of Study Visit 5, the subject will exit the study. A summary of all study assessments per visit can be found in Appendix 4 (Schedule of Visits and Procedures).

Figure 2 Study Design



3.2 Rationale for Study Design and Control Group

AR-15512 is a TRPM8 receptor agonist that modulates activation of cold thermoreceptor nerve terminals of the cornea leading to potentially a dual role mechanism for the treatment of DED; increased tear production and reduction of ocular discomfort and pain. Both pre-clinical and clinical findings support this hypothesis.

In vivo topical administration of AR-15512 was shown to increase tear production and blink rate in guinea pigs and TRPM8 knockout mice are characterized by dramatically reduced basal tearing and an abrogated cold responsiveness without any effect on nociceptor-mediated irritative tearing (Dhaka 2007).

Data from a recently completed Ph1/2a study in subjects with DED provided initial proof of concept for AR-15512 in the treatment of DED. [redacted]

The results of the Phase 2b clinical study will be used to optimize future study designs.

3.3 Study Duration and Dates

The approximate duration of subject participation is approximately 14 weeks (14 days vehicle run-in period before randomization followed by 12 weeks of randomized treatment administration).

4. STUDY POPULATION SELECTION

4.1 Study Population

This study is anticipated to enroll approximately 360 subjects with DED as defined below in Sections 4.2 and 4.3 so as approximately 324 subjects complete Day 84. 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
3. Have used, and/or desired to use artificial tears for DED symptoms within 2 months prior to the Screening visit

7. BCVA 20/200 (+0.70 LogMAR) or better in both eyes at both the Screening and Baseline visits
8. Good general and ocular health, as determined by the investigator using medical history, ophthalmic examination and history, blood chemistry and hematology, urinalysis and vital signs (heart rate and blood pressure) at the Screening visit
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) as specified below 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, likely interfere with the interpretation of the study results or subject safety, such as: significant corneal or conjunctival scarring; pterygium or nodular pinguecula; conjunctivitis, or inflammation not associated with DED; anterior (epithelial) basement membrane

corneal dystrophy or other clinically significant corneal dystrophy or degeneration; evidence of keratoconus; etc. (Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed.)

2. Current evidence of other significant ophthalmic disease requiring topical medication (e.g. glaucoma, ocular hypertension), 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. History of ocular surgery within 1 year prior to the Screening visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision)
4. Have had a corneal transplant in either or both eyes
5. Use of contact lenses in either eye within 7 days prior to the Screening visit or planned use during the study
6. Punctal or intracanalicular plug present in either eyelid within 1 year prior to the Screening visit or anticipated plug insertion or occlusion at any time during the study
7. Use of artificial tears within 2 hours prior to the Screening visit or anticipated use during the study
8. Regular use of lid hygiene within 14 days prior to the Screening visit or any planned use during the study
9. Regular use of any topical ocular medications (including use of ocular cyclosporine or other prescription ophthalmic solution for DED (e.g., Restasis®, Cequa™, Xiidra®), topical ocular corticosteroid- or non-steroidal-anti-inflammatory agents, glaucoma medications, eye whitening products (e.g., Visine®, Lumify®), topical antibiotics, topical antihistamines, mast cell stabilizers or other over-the-counter [OTC], herbal, prescription, or nutritional supplements with the exception of artificial tears), within 30 days prior to the Screening visit or anticipated use during the study. Note: Occasional (as needed) > 24 hours prior to the Screening Visit may be permitted
10. Use of medications associated with 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 90 days prior to the Baseline Visit or anticipated use during the study
11. Use of systemic corticosteroids started < 90 days prior to the Baseline Visit or a change in dosage is anticipated during the study. Note: Non-ocular topically applied corticosteroids (including nasal sprays and inhalers) will be permitted during the study and the dose is not required to be stable
12. Use of TrueTear® within 45 days of the Screening visit or anticipated use during the study
13. Use of lid heating therapy (i.e., LipiFlow®, iLUX®) or Meibomian gland probing/therapeutic expression within 1 year prior to the Screening visit or anticipated during the study

14. Use of systemic immunomodulators (e.g., hydroxychloroquine, methotrexate, cyclosporine) started < 90 days prior to the Baseline Visit or a change in dosage is anticipated during the study
15. Any systemic medication known to cause ocular drying (e.g. antihistamines, antidepressants, beta-blockers) started < 14 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Occasional (as needed) use of medications such as systemic antihistamines will be permitted
16. 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
17. At the Screening visit, at the investigator's discretion, have active or uncontrolled, severe:
    a. Systemic allergy
    b. Chronic seasonal allergies at risk of being active during the study
    c. Rhinitis or sinusitis
18. 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.)
19. Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to the Baseline Visit
20. Known allergies or sensitivity to the study interventions or study diagnostic agents including sodium fluorescein, lissamine green, etc.
21. Positive pregnancy test at Screening or Baseline visits or currently breastfeeding or plans to become pregnant or breastfeed during the study
22. Women of childbearing potential who are not using a medically acceptable form of birth control
23. 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
24. Employees directly involved in the AR-15512-CS201 trial at the clinical site.

4.4 Study Eye Criteria

The study subject must have one eye (the same eye) meeting all the inclusion criteria (Section 4.2) and none of the exclusion criteria (Section 4.3). 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 higher pre-CAE Ora Calibra ODS score at the Baseline visit. If both eyes qualify and have the same pre-CAE Ora Calibra ODS score, then study eye will be defined as

the eye with the lowest anesthetized Schirmer score at the Baseline visit. If both eyes still qualify, the right eye will be designated as the study eye.

5. STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Study Drug

AR-15512 ophthalmic solution is a sterile, preservative-free, isotonic, buffered aqueous solution containing AR-15512 (0.0014% or 0.003%), 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.

Study drug will be provided in masked identical kits:

- AR-15512 ophthalmic solution, 0.0014%
- AR-15512 ophthalmic solution, 0.003%

5.1.2 Vehicle (Placebo) or Control Drug

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 study drug.

5.2 Treatments Administered

AR-15512 (0.0014% and 0.003%) as well as AR-15512 vehicle will be provided as single use blow-fill-seal containers of extruded polyethylene.

5.3 Selection and Timing of Dose for Each Patient

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

Following the vehicle run-in period, those subjects who requalify at the Baseline visit, will be randomized into 3 groups, in a 1:1:1 ratio within each site, as follows:

- AR-15512 0.0014% (N = 120)
- AR-15512 0.003% (N = 120)
- AR-15512 vehicle (N = 120)

Subjects will be re-instructed on proper administration procedures at the Baseline visit. Subjects will be instructed to administer their randomized study treatment 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).

[redacted]

5.4 Method of Assigning Patients to Treatment Groups

All subjects will be centrally assigned to randomized study treatment using an interactive web response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS 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 14 days (vehicle run-in period). Following the run-in period, all subjects who requalify at the Baseline visit (Day 1 [Visit 2]), will be randomized in a 1:1:1 ratio, within each site, to receive AR-15512 0.0014% : AR-15512 0.003% : AR-15512 vehicle. The IWRS will provide the site with the specific kit number(s) for each randomized subject at the time of randomization. Sites will dispense the study treatment according to the IWRS instructions and the Schedule of Visits and Assessments (Appendix 3).

5.5 Masking

During the vehicle run-in period, the subject will be masked. During the randomized treatment period, the investigator and site staff performing eligibility / efficacy and safety assessments and the subjects will be masked. 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 (0.0014%), AR-15512 (0.003%) and AR-15512 vehicle will be provided in identical single-use blow-fill-seal containers.

The staff members who administer the treatment drop at each visit will not be allowed to participate in any efficacy or safety-related assessments post-drop administration.

5.6 Unmasking

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

Treatment 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 treatment 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 treatment assignment after an emergency situation, the Investigator should contact the Medical Monitor or designee. Only after consultation with the Medical Monitor will a decision be made as to whether or not the treatment for the subject should be unmasked. The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the masking on the remaining subjects intact.

5.7 Concomitant Therapy

Any therapy or intervention (including OTC, prescription medicines, vitamins and herbal supplements) that the subject is receiving at the time of screening or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

From the Screening visit to the end of the study (Visit 5 or early termination), site staff will question each subject specifically on the use of concomitant therapies and interventions. Site staff must notify Aerie immediately if a subject consumes or applies any concomitant treatments or interventions that are not permitted by the protocol.

Use of the following as concomitant therapy or interventions during the study is prohibited:

- Regular use of any topical ocular medications (including use of ocular cyclosporine or other prescription ophthalmic solution for DED (e.g., Restasis®, Cequa™, Xiidra®), topical ocular corticosteroid- or non-steroidal-anti-inflammatory agents, glaucoma medications, eye whitening products (e.g., Visine®, Lumify®), topical

antibiotics, topical anti-histamines, mast cell stabilizers or other OTC, herbal, prescription, nutritional supplements or artificial tears)

- Systemic immunomodulators (e.g., hydroxychloroquine, methotrexate, cyclosporine) started < 90 days prior to the Baseline Visit or a change in dosage is anticipated during the study
- Cyclosporine administered through any route
- Systemic corticosteroids administered through any route (e.g. oral or IV) started < 90 days prior to the Baseline Visit or a change in dosage is anticipated during the study
- Medications associated with the treatment of severe DED and/or Meibomian gland disease (e.g., oral pilocarpine, oral cevimeline, oral macrolides, oral tetracyclines, oral tetracycline derivatives, and oral retinoids)
- Contact lens wear in either eye
- Punctal or intracanalicular plugs
- Lid-heating therapy (ie, LipiFlow, iLUX, etc.), Meibomian gland probing, or therapeutic Meibomian gland expression
- Regular use of lid hygiene
- Any systemic medication known to cause ocular drying (e.g. antihistamines, antidepressants, beta-blockers) started < 14 days prior to the Screening visit or a change in dosage is anticipated during the study. Occasional (as needed) use of medications such as systemic antihistamines will be 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 (as needed) use of cold/flu medications that **do not** contain antihistamines will be permitted. Cold/flu medications that **do** contain antihistamines are discouraged but will be permitted (please refer to the Allowed Concomitant Medication List). In addition, all systemic medications (including OTC and herbal), not listed in Exclusions are allowable. Skin care products containing retinoids are allowable.

5.8 Restrictions

5.8.1 Prior Therapy

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:

Table 1 Required Washout for Prohibited Therapies or Interventions Prior to the Screening or Baseline Visit

Treatment/Intervention	Washout Required Prior to the Screening Visit
Artificial tears	2 hours
Contact lenses	7 days
Punctal or intracanalicular plugs	1 year
Regular use of topical ocular medications (including ocular cyclosporine or other prescription ophthalmic solution for DED (e.g., Restasis®, Cequa™, Xiidra®), topical ocular corticosteroid- or non-steroidal-anti-inflammatory agents, glaucoma medications eye whitening products (e.g., Visine®, Lumify®) topical antibiotics, topical anti-histamines, mast cell stabilizers or other OTC, herbal, prescription, or nutritional supplements). Note: Occasional (as needed) > 24 hours prior to the Screening Visit may be permitted	30 days
Lid-heating therapy, Meibomian gland probing, or therapeutic Meibomian gland expression	1 year
TrueTear®	45 days
Regular use of lid hygiene	14 days
Any systemic medication known to cause ocular drying (e.g. antihistamines, antidepressants, beta-blockers) started < 14 days prior to the Screening visit or a change in dosage is anticipated during the study. Note: Occasional (as needed) use of medications such as systemic antihistamines will be permitted	14 days[a]
Treatment/Intervention	**Washout Required Prior to the Baseline Visit**
Medications associated with 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	90 days
Systemic immunomodulators (e.g., hydroxychloroquine, methotrexate, cyclosporine) started < 90 days prior to the Baseline Visit or a change in dosage is anticipated during the study	90 days[b]
Systemic corticosteroids (IV and oral) started < 90 days prior to the Baseline Visit or a change in dosage is anticipated during the study	90 days[b]

a. The use of these therapies is allowed during the study provided that the dosing regimen is stable for at least 14 days prior to the Screening visit and does not change at any time during the study duration. The total time for washout if one of the systemic medications known to cause ocular dryness was stopped is 14 days relative to Screening visit.

b. The use of these therapies is allowed during the study provided that the dosing regimen is stable for at least 90 days prior to the Baseline Visit and does not change at any time during the study duration. The total time for washout if one of these medications was stopped is 90 days relative to Baseline Visit

5.8.2 Fluid and Food Intake

None

5.8.3 Subject Activity Restrictions

Subjects are to administer their morning dose of randomized treatment on the days of Visits 2, 3, 4 and 5. Subjects are not to administer the evening dose of the randomized treatment on the days of Visits 2, 3, and 4 since it is administered during the clinic visit.

5.8.4 Females of Childbearing Potential and Acceptable Contraceptive Methods

An adult woman is considered of childbearing potential unless she is at least 1-year post-menopausal (defined as 12 consecutive months with no menses without an alternative medical cause) or 3 months post-surgical sterilization (includes hysterectomy, bilateral oophorectomy, or bilateral tubal ligation). All females of childbearing potential must have a negative urine pregnancy test result at the Screening, Baseline and Exit Visits. Pregnancy tests must be negative for the subject to receive study intervention. Subject must not intend to become pregnant during the study and must properly use a reliable method of contraception. The following methods of contraception are considered reliable: hormonal contraceptives, intrauterine device, surgical sterilization, partner with vasectomy, or sexual abstinence. For male subjects in the study, condoms are considered a reliable method of contraception.

If pregnancy occurs during the study, every attempt will be made to collect data on the pregnancy of female subjects. Signature of a separate consent form will be requested of the pregnant woman. Information on pregnant partners of study subjects will not be collected.

Every attempt will be made to collect data regarding the newborn child born to a female subject with parent/guardian permission. One parent or the legal guardian will be requested to provide permission for the minor to participate in this part of the research.

5.9 Permitted Interventions

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

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 (as needed) use of and cold/flu medications that **do not** contain antihistamines will be permitted. Cold/flu medications that **do** contain antihistamines are discouraged but will be permitted (please refer to the Allowed Concomitant Medication List).
- Skin care products containing retinoids are permitted.

Any medication taken during the study between the date of the first dose of randomized study treatment and the date of the Exit visit or Early Termination visit should be recorded in the case report form (CRF) as a concomitant medication.

5.10 Treatment Compliance

For Visit 1, the morning dose will be administered in clinic by the subject under supervision from site personnel. For Visits 2, 3 and 4, the second dose will be administered by designated site personnel; all other doses will be administered by the subject.

In-between office visits, study compliance will be monitored by counting the number of used and unused vials dispensed and returned. Subjects will be instructed on instillation and storage of study treatment at the end of Visits 1, 2, 3, and 4, as well as provided written instructions. The subject's used and unused study treatment vials will be collected at each visit from Visit 2 up to and including Visit 5 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 deviation should be recorded.

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 treatment dispensed to each subject, the amount of study treatment returned to the site, and the dates of each.

5.11 Packaging and Labeling

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

The products for each individual treatment assignment will be packaged into identical subject kits; each subject kit will contain one of 3 treatments: AR-15512 ophthalmic solution 0.0014%, 0.003% or AR-15512 ophthalmic solution, vehicle.

5.12 Storage and Accountability

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

5.12.1 Receipt and Disposition of Study Medication

Study treatments will be shipped to the Investigator's site from a central depot. A study staff member at the Investigator's site who is not involved in conducting any efficacy or safety procedures will verify study treatment shipment records by comparing the shipping documentation accompanying the study treatment to the study treatment actually received at the Investigator's site. 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 treatment at the Investigator's site is the only site staff member permitted to distribute investigational product and also has sole responsibility to account for all returned used, partially used and unused vials and kits of study treatment. The study treatment(s) must not be used outside this protocol.
An Investigational Product Accountability Log will be kept at each clinical site.

5.12.2 Return of Study Medication

When the study is completed or is terminated by the Sponsor, all study materials including used and unused study treatment 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 treatment and return them to the clinical site. All study treatment 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 treatment. This site staff member at the Investigator's site will complete a study treatment returns form or equivalent that will be signed by the Investigator or designee prior to returning the used and unused study treatment kits /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 and Medical History

Demographic data and any ongoing medication use 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.

6.3 Vital Signs

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

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

6.4 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.

The clinical laboratory results must be reviewed by the Investigator prior to subject enrollment, and the tests cannot be indicative of any clinically significant or uncontrolled disease in the opinion of the Investigator.

6.4.2 Pregnancy Testing

Urine pregnancy tests for women of childbearing potential (WOCBP; defined in Section 5.8.4) are required at Screening, Baseline and Exit Visits. Pregnancy tests must be negative for the subject to receive study treatment.

6.4.3 Sample Collection, Storage and Shipping

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

6.5 Dispensing Investigational Product

Study-related site personnel will be cautioned that any used or unused study treatment 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 treatment 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 treatment according to the IWRS. The responsible study staff will account for all used, partially used and unused study kits / vials by maintaining an Investigational Product Accountability log.

Details of timing and procedures for dispensing Investigational Product are found in the Pharmacy Manual.

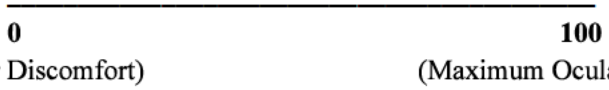
6.6 Efficacy Assessments

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 (pre-CAE) and "now/currently" (post-CAE), each on a separate VAS: *ocular discomfort (ODS), eye dryness (EDS), ocular pain (OP)*. 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 the scale will be 100 mm and will be similar to the following depiction for ocular discomfort (Figure 3).

While in the CAE, subjects will be reassessed at 5-minute intervals on only the ODS-VAS based on how they feel "now/currently".

Figure 3 Ocular Discomfort: Visual Analog Scale



6.6.2 Symptom Assessment in Dry Eye (SANDE) Questionnaire

The SANDE questionnaire (Schaumberg 2007) is comprised of 2 unique VAS scales to assess the frequency and severity of DED symptoms. [redacted] The assessment line length of the scale will be 100 mm and will be similar to the following depiction (Figure 4). Higher scores indicate greater frequency or severity.

The Global 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 4 SANDE Questionnaire

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

1. **Frequency of symptoms:**

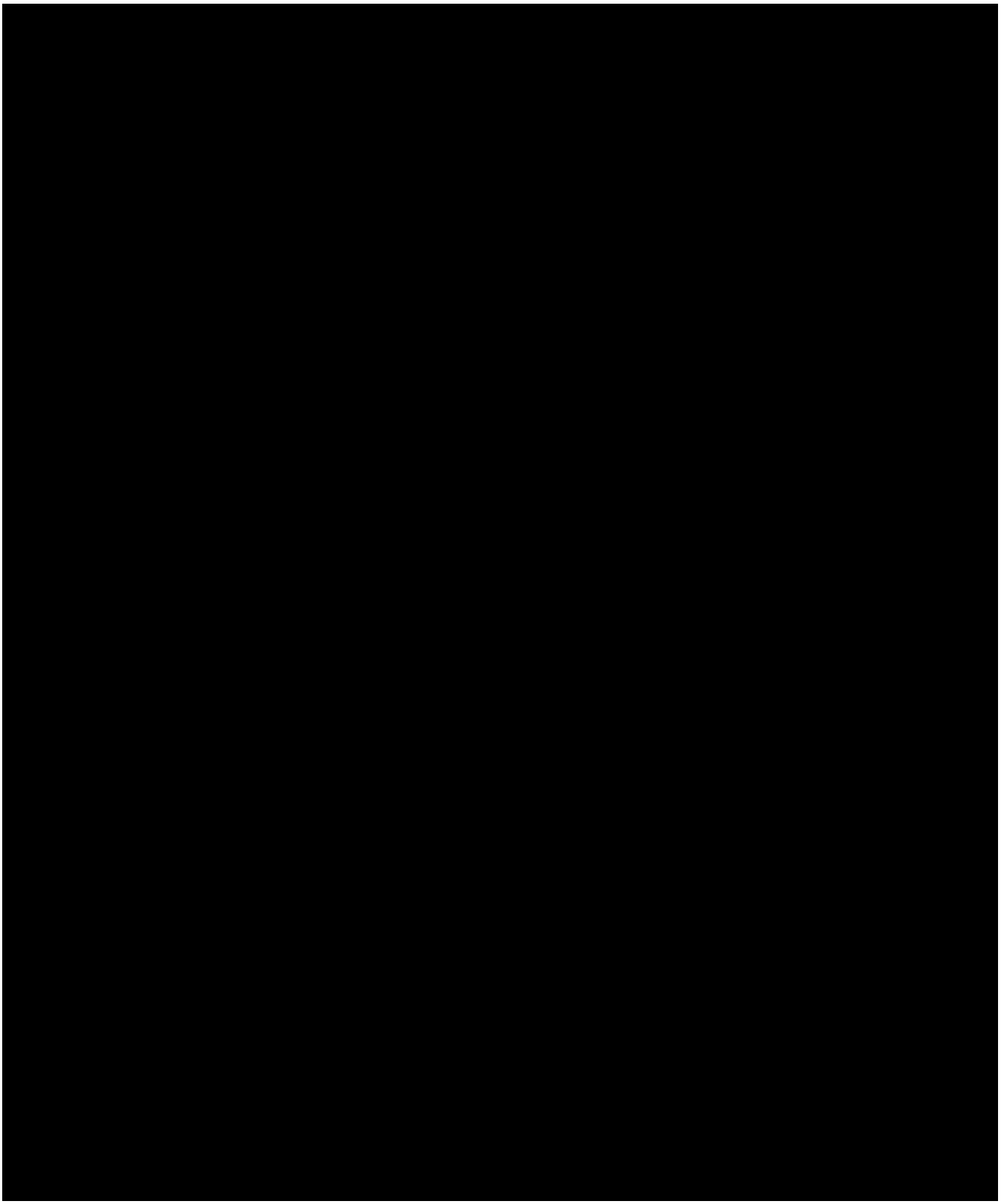
   Place a single vertical mark on the horizontal line to indicate how often, on average, your eyes feel dry and/or irritated.

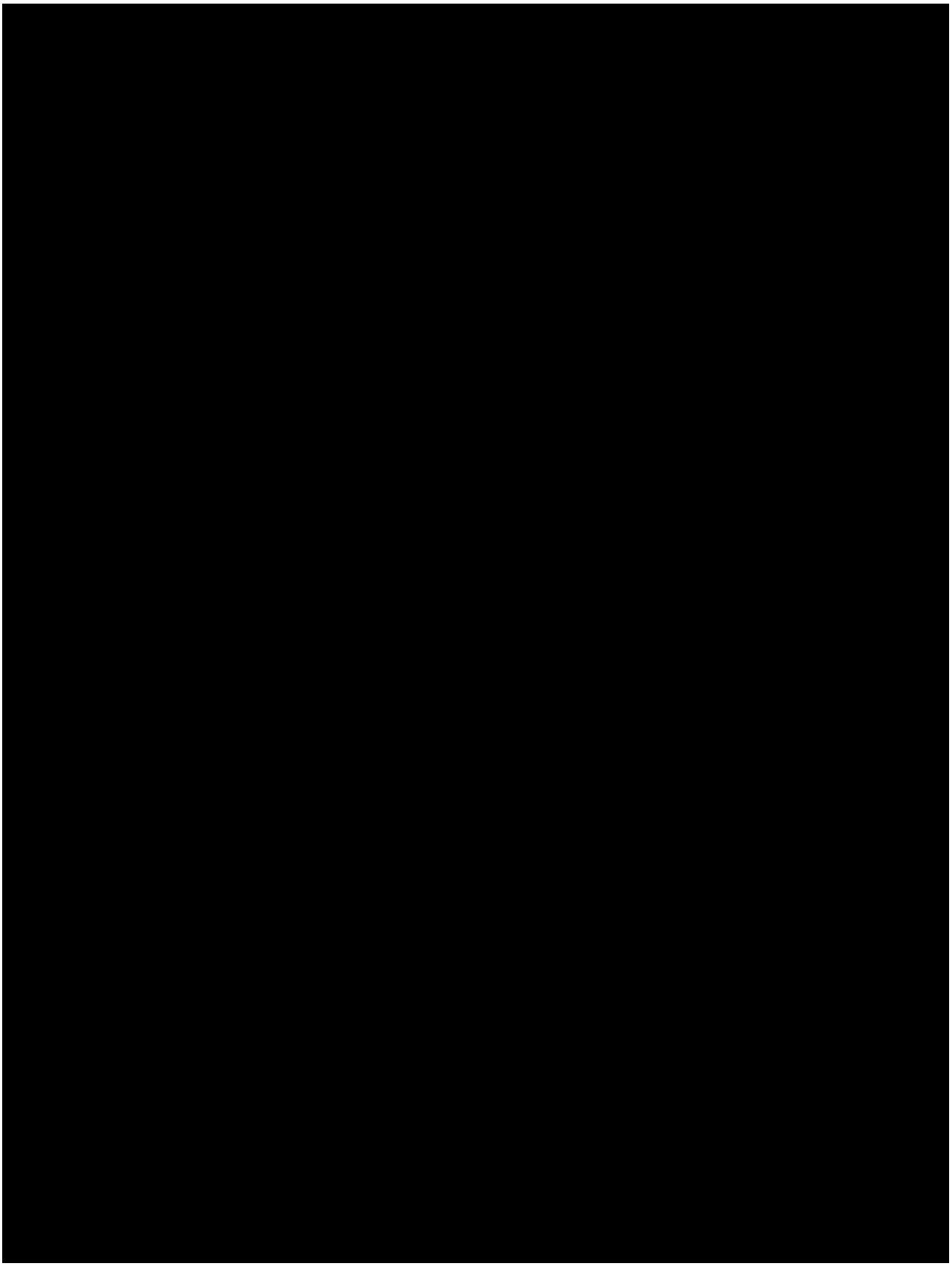
   1. Frequency Rarely All the time

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



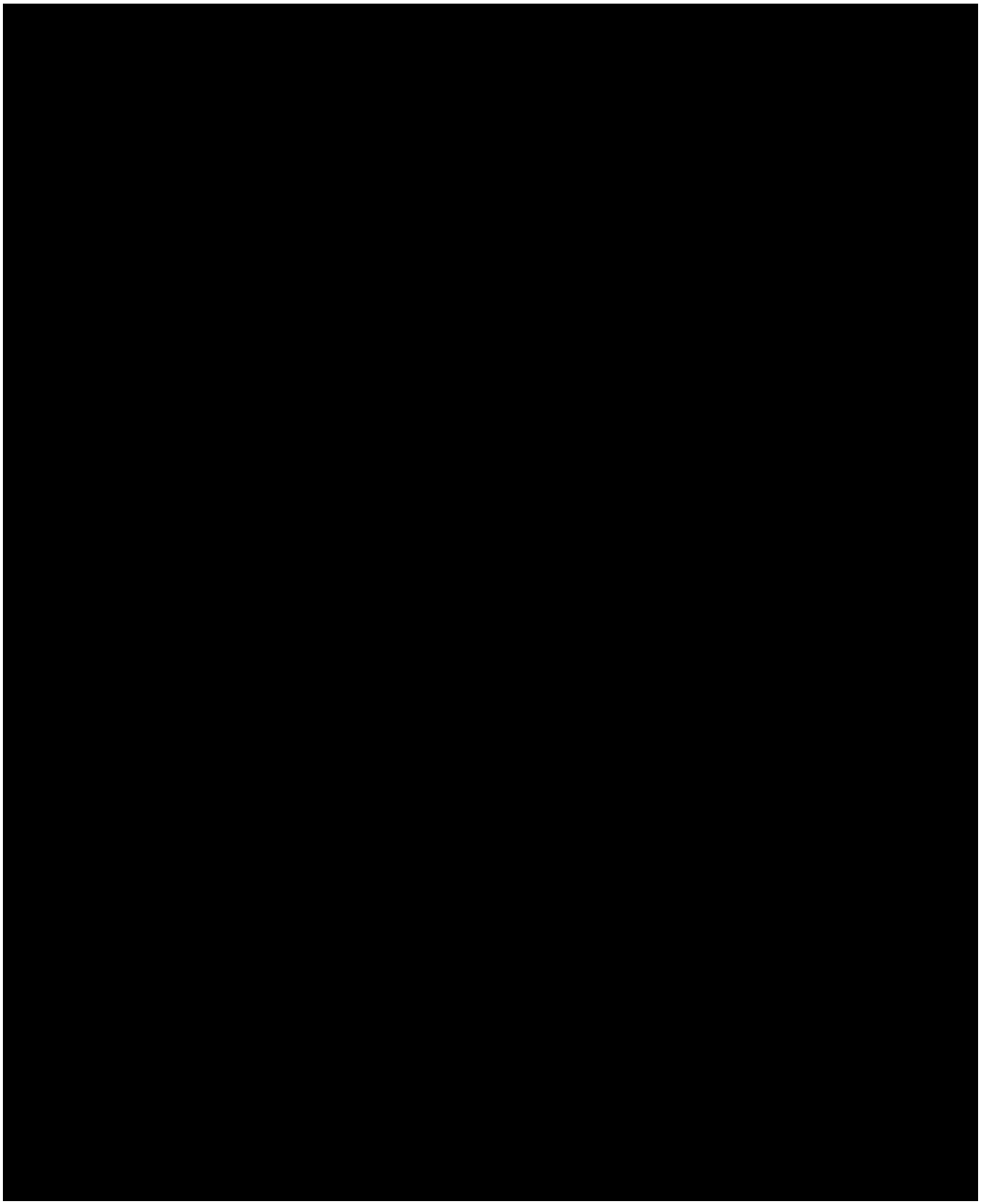


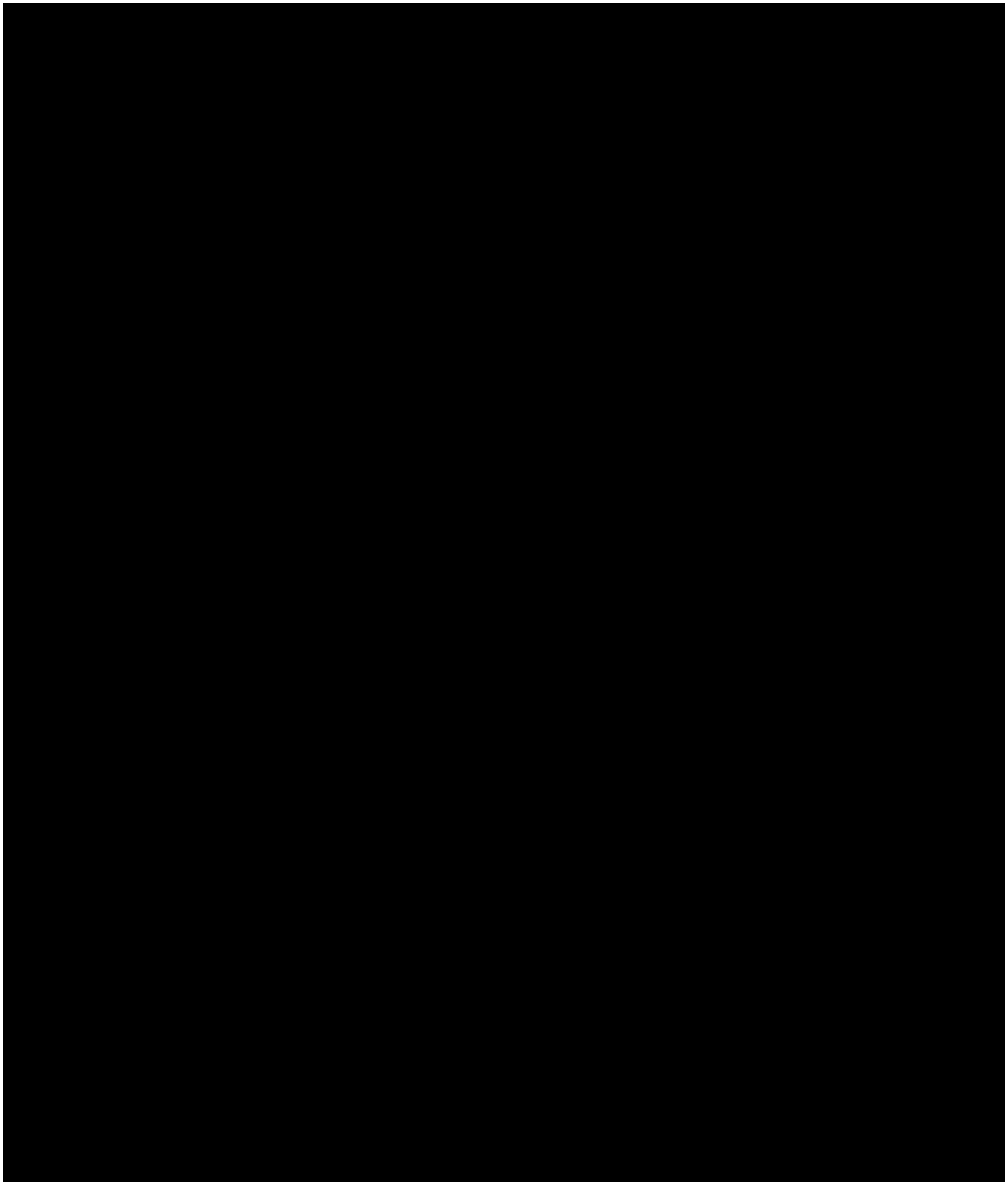
[redacted]

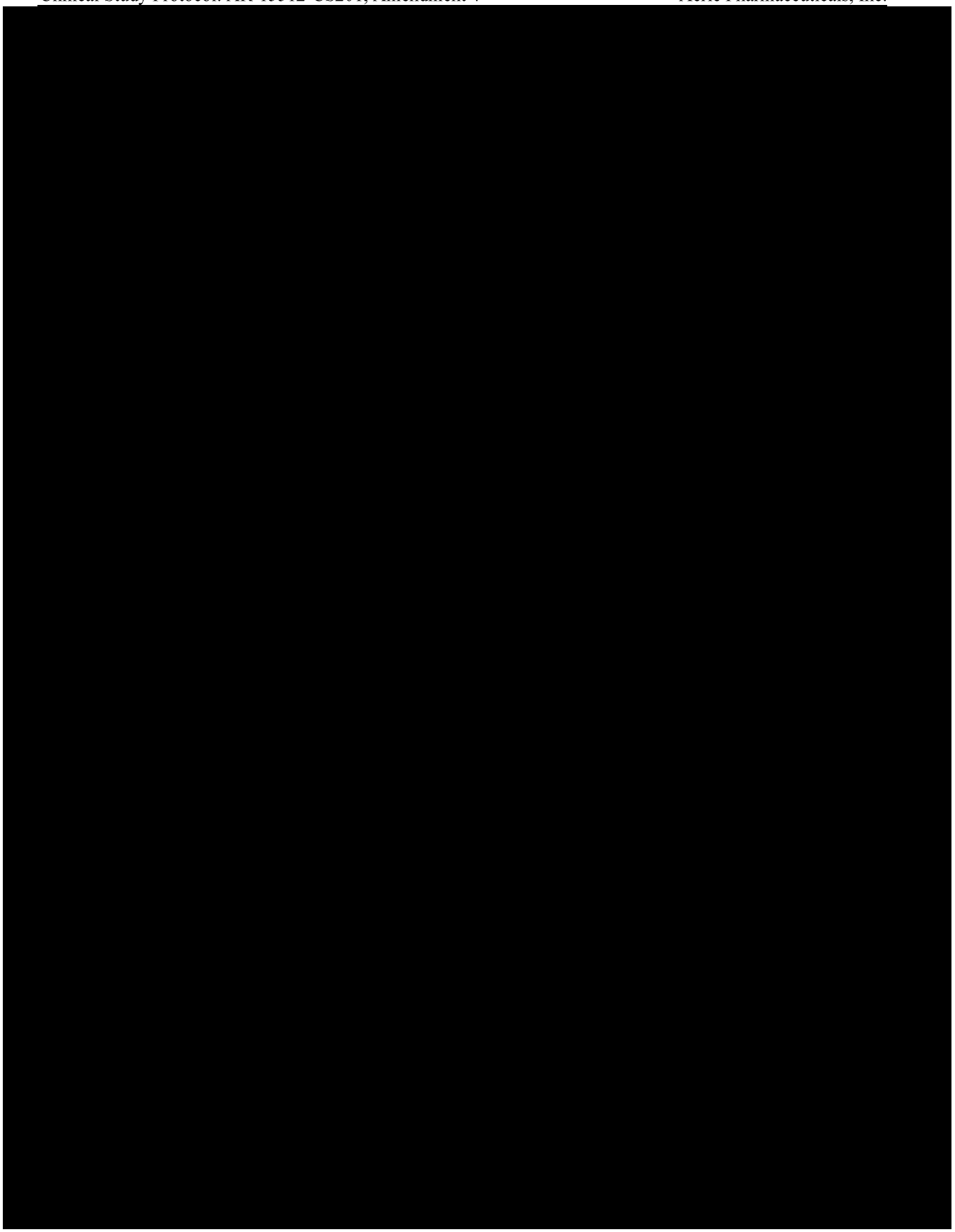
6.6.6 Anesthetized Schirmer Test

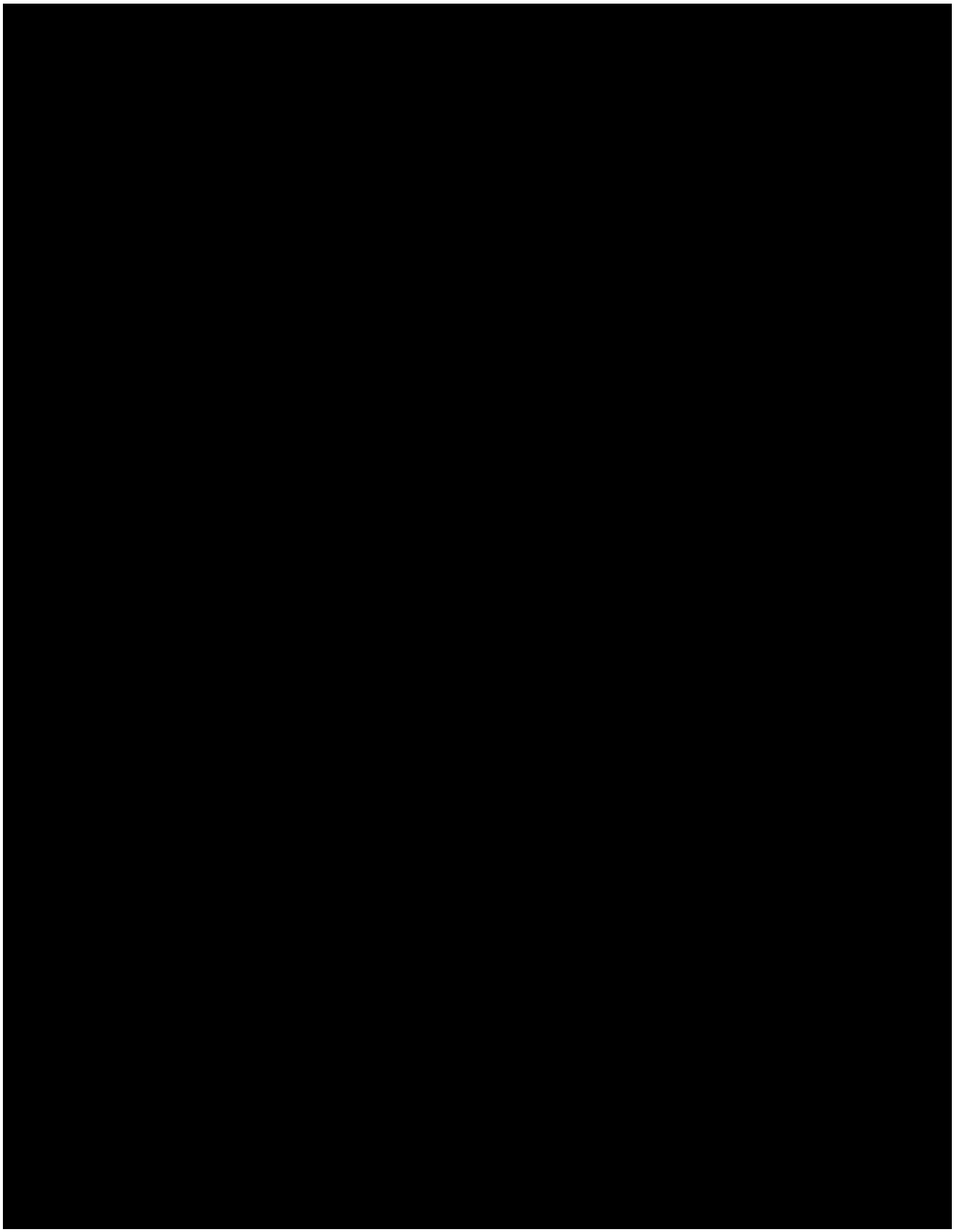
The test should be performed in a room with no direct air or sunlight on the subject's face by the Investigator or designated sub-Investigator. Every effort should be made to ensure the same individual performs this assessment for a given subject at each applicable visit. Under ambient light, the subject will be instructed to look forward and to blink normally during the course of the test. Topical anesthetic drops such as 0.5% proparacaine hydrochloride or equivalent should be instilled in both eyes of the subject. The subject will be instructed to keep the eyes gently closed for 1 minute. After opening the eyes and allowing the eyes to recover for approximately 1 additional minute, excess moisture in the inferior fornix can be gently removed with a spear. Schirmer's strips will be placed in each eye at the junction of the middle and lateral thirds of the lower eye lid. Under ambient light, the subject will be instructed to look forward and to blink normally during the course of the test. The timer should be started immediately after the strips are inserted. The Schirmer's strips should remain in place until 5 minutes have elapsed or both strips have reached maximum score. After 5 minutes, strips will be removed from both eyes and the amount of wetting will be recorded. As the tear front may continue advancing a few millimeters after it has been removed from the eyes, it is important to read the tear front immediately after removal. Only whole numbers are to be recorded, rounding up to the nearest whole number if the tear front is at or greater than the half millimeter mark.

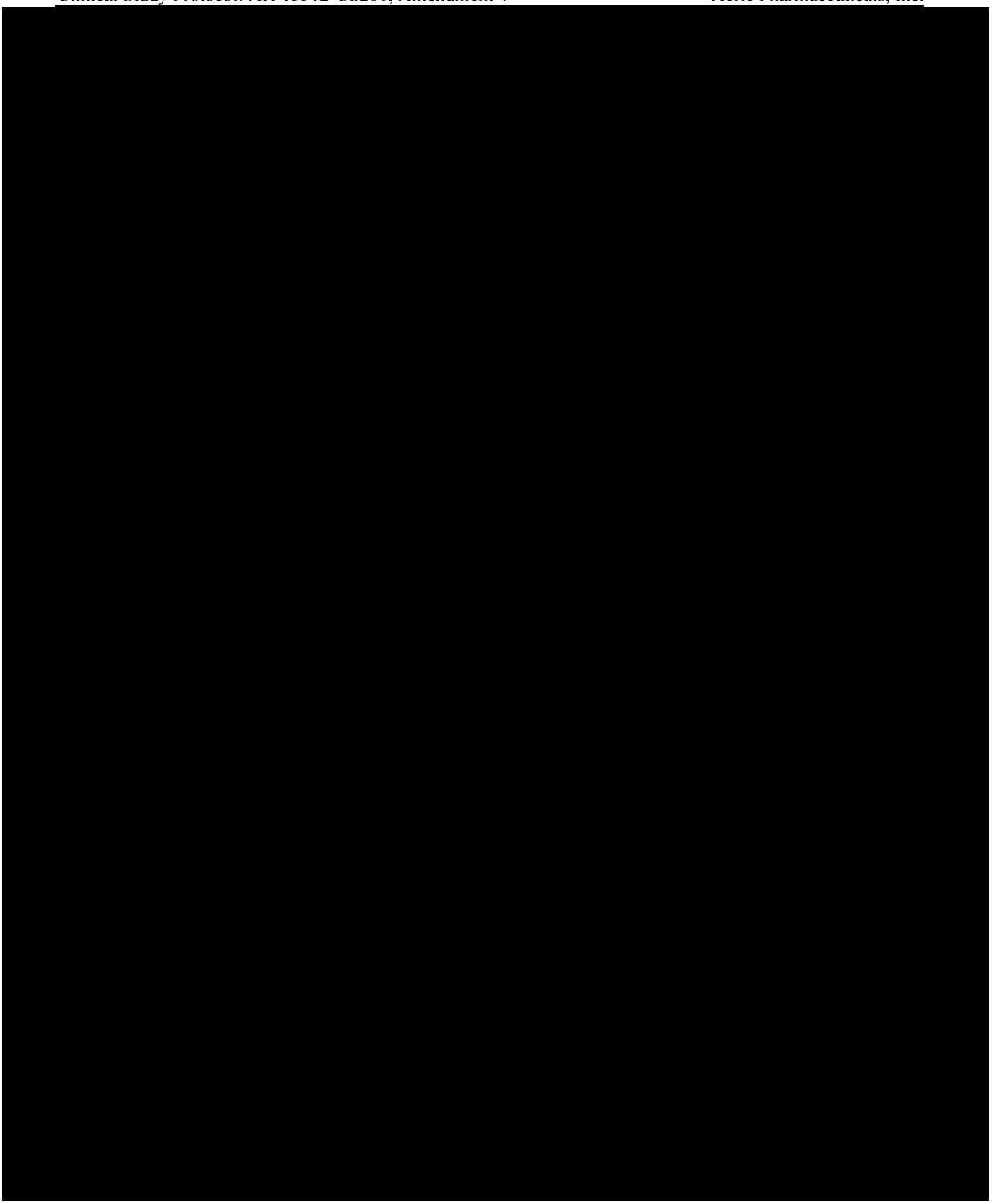
[redacted]

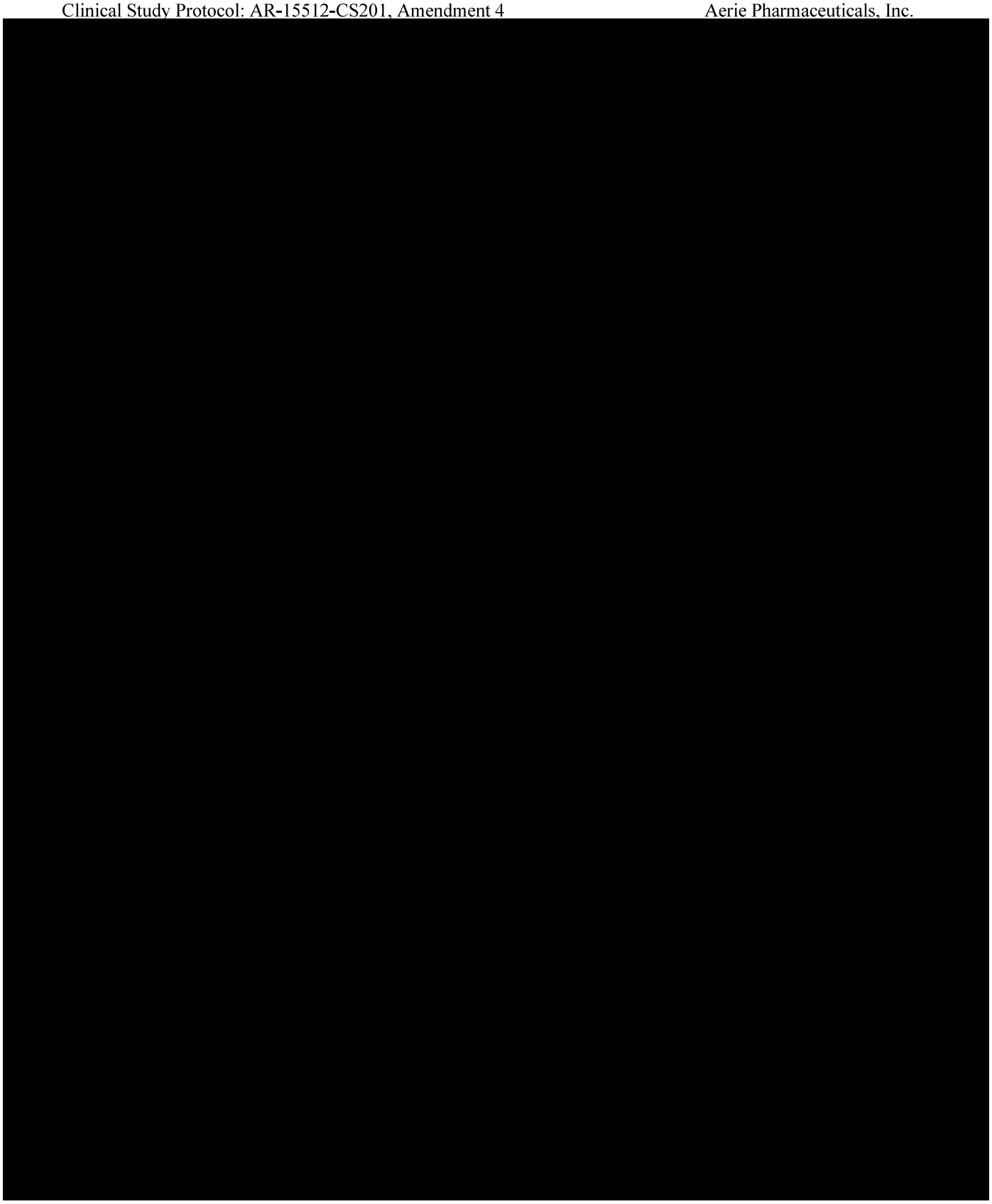












[redacted]

6.7.2 Controlled Adverse Environment (CAE) Exposure

Subjects will be exposed to the CAE for approximately 90 minutes during each CAE visit (Visits 1, 2, and 5 as well as Visit 4 at selected sites). The ODS-VAS and Ora Calibra ODS scores will be collected upon entering the CAE and approximately every 5 minutes thereafter.

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

[redacted]

6.8 Safety Assessments

6.8.1 Best-Corrected Visual Acuity (BCVA)

Visual Acuity Procedures

LogMAR visual acuity must be assessed using an ETDRS Series 2000 chart. The procedure used will be consistent with the recommendations provided for using an ETDRS eye chart. Visual acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit lamp examination). Subjects should use the most recent correction to attain their BCVA; if they forget their spectacles, this prescription can be placed in a trial frame.

Equipment

An ETDRS Series 2000 visual acuity chart must be used. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the subject viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only ETDRS Series 2000 Charts and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and be well illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, s/he should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be

asked to read slowly, so as to achieve the best identification of each letter. S/he is not to proceed to the next letter until s/he has given a definite response.

If the subject changes a response (e.g., 'that was a "C" not an "O"') before s/he has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the subject says s/he cannot read a letter, s/he should be encouraged to guess. If the subject identifies a letter as one of two letters, s/he should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and including the last line read. This total sum represents the logMAR visual acuity for that eye.

Example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR visual acuity	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (i.e., a subject broke his/her glasses), the reason for the change in correction should be documented.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.32 or greater in logMAR score) from the Screening Visit (Visit 1) should be evaluated by the Investigator as a potential AE.

6.8.2 Biomicroscopy and Dilated Fundus Exam by Slit Lamp

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:

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

External magnification and biomicroscopy will be performed using a slit-lamp. Magnification will be consistent with standard clinical practice. The subject will be seated.

Dilated Fundoscopy:

Dilated fundus exams will be performed 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.

6.8.3 Intraocular Pressure (IOP)

The IOP must be measured 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 uses the same device for IOP measurement for a given subject. A Goldmann applanation tonometer affixed to a slit-lamp is the preferred device for IOP measurement.

6.9 Adverse Events Assessments

6.9.1 Performing Adverse Event (AE) Assessments

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.

All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective CRF. AEs should be documented from the time the subject provides informed consent and throughout the study. If a serious or non-serious AE/adverse reaction is unresolved at the time of the exit date, efforts will be made to follow up until the AE/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

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

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 drug in humans, whether or not considered drug related.

- *Suspected adverse reaction (SAR)*: 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. SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by the administration of a drug.

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

- *Serious adverse event (SAE) or serious suspected adverse reaction (SSAR)*: an AE or SAR 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, in 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.

- *Unexpected AE or unexpected SAR*: an AE or SAR 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. 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 SARs 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.

Note: Any medical condition present prior to informed consent and prior to administration of the study medication which remains unchanged or improved should not be recorded as an AE at subsequent visits.

Note: 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 AEs.

6.9.3 Timing for Reporting Adverse Events

The AEs occurring during the study must be documented, regardless of the assumption of a causal relationship. 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/adverse reaction is unresolved at the time of exit, efforts will be made to follow up until the AE/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.

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

1. Action Taken with Study Drug:
    - None
    - IP Discontinued
    - IP Interrupted
2. AE Outcome:
    - Fatal

- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown/Lost to follow-up

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 6.9.7 for further information on SAEs, SSARs, and SUSARs).

6.9.5 Relationship

A relationship between the AE and the study medication 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 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 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 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 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 SARs are considered "unexpected" if they **are not** listed in 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 SARs 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 IP. The AEs and adverse reactions that are both unexpected and serious should be reported in an expedited fashion to the Sponsor and / or contract research organization (CRO).

6.9.7 Serious Adverse Events (SAEs), Serious Suspected Adverse Reactions (SSARs) or Suspected Unexpected Serious Adverse Reactions (SUSARs)

6.9.7.1 Reporting SAEs or SSARs

An Investigator must immediately (i.e., within 24 hours) report any SAE or SSAR (see Section 6.9.2 for definitions) to the Sponsor or its CRO representative, whether or not considered drug-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 SSAR 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.

SAEs and SSARs must be reported to the IRB according to the IRB requirements.

6.9.7.2 Reporting Serious Unexpected Suspected Adverse Reactions (SUSARs)

The Investigator must immediately (i.e., within 24 hours) report SUSARs that occur or are observed during the study or at the subject's last study visit. In the event of SUSAR, the site must notify the Medical Monitor for the study using the 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.

Reports will be evaluated by the Medical Monitor. The FDA, IRB and Investigators at each of the study sites will be informed as required.

6.9.8 Pregnancy Reporting

Pregnancies occurring in subjects enrolled in the study or in their partners must be reported and followed to outcome. While pregnancy itself is not considered to be an AE or SAE, pregnancy reports are tracked by the Sponsor or its CRO representative. Premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE. Other pregnancy complications should be reported as SAEs, if they meet serious criteria. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality.

The Investigator must complete the pregnancy report form and fax or email the form to the Sponsor or its CRO representative within 1 business day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the pregnancy report form is to be completed and submitted by fax or email to the Sponsor or its CRO representative.

Pregnancies occurring from the time of consent through the subject's last study visit are to be reported.

6.9.9 Reporting Serious Adverse Events, Serious Suspected Adverse Reactions (SSARs) or Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Investigator must report an SAE, SSAR, or SUSAR occurring at his/her site to the Sponsor or its CRO representative regardless of causality.

[redacted]

6.10 Removal of Subjects from the Study or Investigational Product

6.10.1 Completed Subject

A completed subject is defined as one who completes all planned study treatments and visits.

6.10.2 Non-completing Subject

A non-completing subject is defined as one who exits the study by their own volition or at the discretion of the Investigator, the Medical Monitor, and/or an Aerie Safety Officer/designee. Any subject may decide to voluntarily withdraw from the study at any time without prejudice. If discontinuation of treatment is necessary, the Investigator will make every attempt to complete all subsequent safety assessments listed for the Early Termination Visit.

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 CRF)
- Withdrawal of Consent
- Non-compliance (e.g., non-adherence to scheduled follow-up visits or use of study treatment)
- Lost to Follow-up
- Pregnancy
- Investigator Decision
- Protocol Deviation
- Death
- Other

6.10.3 Actions after Discontinuation

All subjects who discontinue study treatment 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.

6.10.4 Discontinuation of the Entire Study

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

6.10.5 Completed Study

The study is completed when the planned enrollment has been completed, and all the enrolled subjects have completed the study. An Aerie representative will be in communication with the investigational sites regarding enrollment.

7. STUDY ACTIVITIES

7.1 Screening Visit (Visit 1; Day -14 (+3*))

- Informed consent
- Inclusion and exclusion criteria
- Demographics
- Medical, ophthalmic, and surgical history
- Prior or concomitant medication review
- Adverse events
- Vital signs (heart rate and blood pressure)
- Urine pregnancy test (WOCBP only)
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- SANDE Questionnaire (VAS)
- Ora Calibra Ocular Discomfort Scale (ODS)
- Best-corrected visual acuity
- Slit-lamp biomicroscopy
- At least 5 minute rest period
- Anesthetized Schirmer test

- A least 10 minute rest period

[redacted]

- CAE exposure
- Inclusion and exclusion criteria
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- Ora Calibra Ocular Discomfort Scale (ODS)
- Slit-lamp biomicroscopy

[redacted]

- Review of qualification
- Hematology, chemistry, and urinalysis
- Intraocular pressure
- Dilated fundus exam
- Dispensing of the study treatment
- In office administration of study treatment
- AE review

* Visit 1 should be scheduled between 11 and 14 days before Visit 2. If absolutely necessary, Visit 2 may be delayed up to 7 days (extending the run-in period to a maximum of 21 days).

7.2 Treatment Period

7.2.1 Visit 2 (Day 1; Baseline) Procedures

- Inclusion and exclusion criteria
- Collection of used and unused study treatment
- Concomitant medication review
- AE review
- Urine pregnancy test (WOCBP only)
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- SANDE Questionnaire (VAS)
- Ora Calibra Ocular Discomfort Scale (ODS)

[redacted]

- Best-corrected visual acuity

[redacted]

- Slit-lamp biomicroscopy

[redacted]

- At least 5 minute rest period
- Anesthetized Schirmer test

[redacted]

- CAE exposure

- Inclusion and exclusion criteria
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- Ora Calibra Ocular Discomfort Scale (ODS)
- Slit-lamp biomicroscopy

[redacted]

- Review of qualification
- Randomization
- Dispensing of Study Treatment
- At least 30 and up to 45 minute rest period
- Pre-drop non-anesthetized Schirmer test
- At least 15 and up to 20 minute rest period
- In office administration of study treatment

[redacted]

- AE review

7.2.2 Visit 3 (Day 14 ± 2) Procedures

- Collection of used and unused study treatment
- Concomitant medication review
- AE review
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)

- SANDE Questionnaire (VAS)
- Ora Calibra Ocular Discomfort Scale (ODS)

[redacted]

- Best-corrected visual acuity
- Slit-lamp biomicroscopy

[redacted]

- At least 10 minute rest period

[redacted]

- Dispensing of Study treatment

[redacted]

- At least 15 and up to 20 minute rest period
- In office administration of study treatment

[redacted]

- AE review

7.3 Visit 4 (Day 28 ± 2) Procedures

- Collection of used and unused study treatment
- Concomitant medication review
- AE review

- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- SANDE Questionnaire (VAS)
- Ora Calibra Ocular Discomfort Scale (ODS)

[redacted]

- Best-corrected visual acuity

[redacted]

- Slit-lamp biomicroscopy

[redacted]

- At least 5 minute rest period
- Anesthetized Schirmer test
- At least 10 minute rest period

[redacted]

- CAE exposure (Selected Sites)
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- Ora Calibra Ocular Discomfort Scale (ODS)
- Slit-lamp biomicroscopy

[redacted]

[redacted]

- Dispensing of Study treatment

[redacted]

- In office administration of study treatment

[redacted]

- AE review

7.4 Visit 5 (Day 84 -5 / +2) Procedures

- Collection of used and unused study treatment
- Concomitant medication review
- AE review
- Urine Pregnancy test (WOCBP only)
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- SANDE Questionnaire (VAS)
- Ora Calibra Ocular Discomfort Scale (ODS)

[redacted]

- Best-corrected visual acuity

[redacted]

- Slit-lamp biomicroscopy

[redacted]

- At least 5 minute rest period

- Anesthetized Schirmer test

- CAE exposure
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- Ora Calibra Ocular Discomfort Scale (ODS)
- Best-corrected visual acuity
- Slit-lamp biomicroscopy

- Intraocular Pressure
- Dilated Fundus Exam
- AE review
- Study Exit

7.5 Early Termination Procedures

- Collection of used and unused study treatment
- Concomitant medication review

- AE review
- Pregnancy test (WOCBP only)
- Symptom Questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)
- SANDE Questionnaire (VAS)
- Ora Calibra Ocular Discomfort Scale (ODS)

[redacted]

- Best-corrected visual acuity
- Slit-lamp biomicroscopy
- Intraocular Pressure
- Dilated Fundus Exam
- Study Exit

7.6 Unscheduled Visits

An unscheduled visit may be any visit to the Investigator other than the specific 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 CRF.

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 Sponsor and Study Monitor. The Investigator will allow the Sponsor or designee to inspect all CRFs; subject records (source documents); signed consent forms; records of study medication receipt, storage, preparation, and disposition; and regulatory files related to this study.

9. PLANNED STATISTICAL METHODS

9.1 Statistical Considerations

9.1.1 General Considerations

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

All summaries will be presented by treatment group.

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

Baseline measures are defined as the last non-missing measure prior to the initiation of randomized study treatment. If a measure is taken both pre-CAE® and post-CAE®, baseline will be the time point matched value.

Change from baseline (CFB) will be calculated as visit – baseline; treatment comparisons will be calculated as AR-15512 – vehicle; and pre to post CAE comparisons will be calculated as post-CAE minus pre-CAE.

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

9.1.2 Unit of Analysis

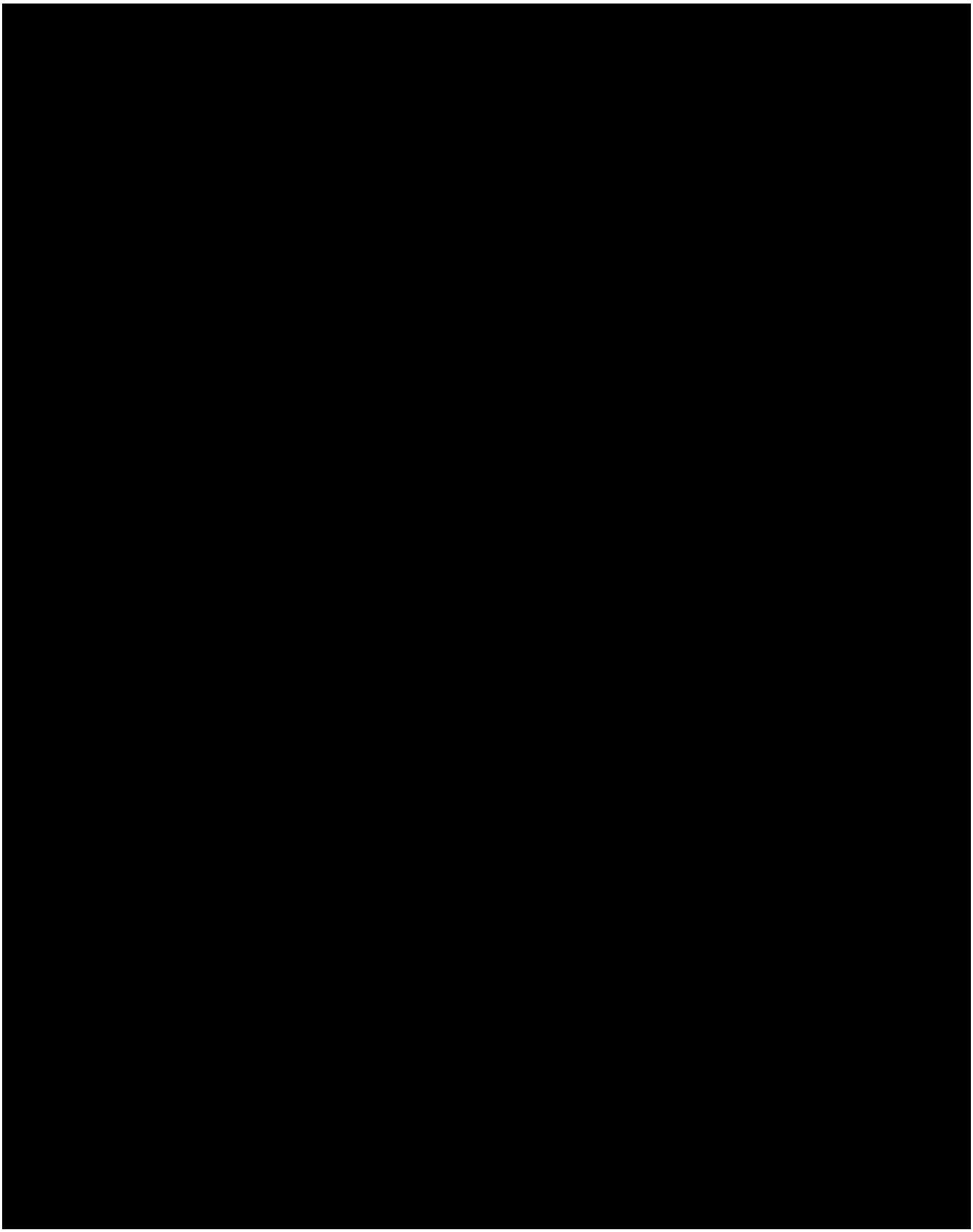
Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the "study eye" as defined by the following:

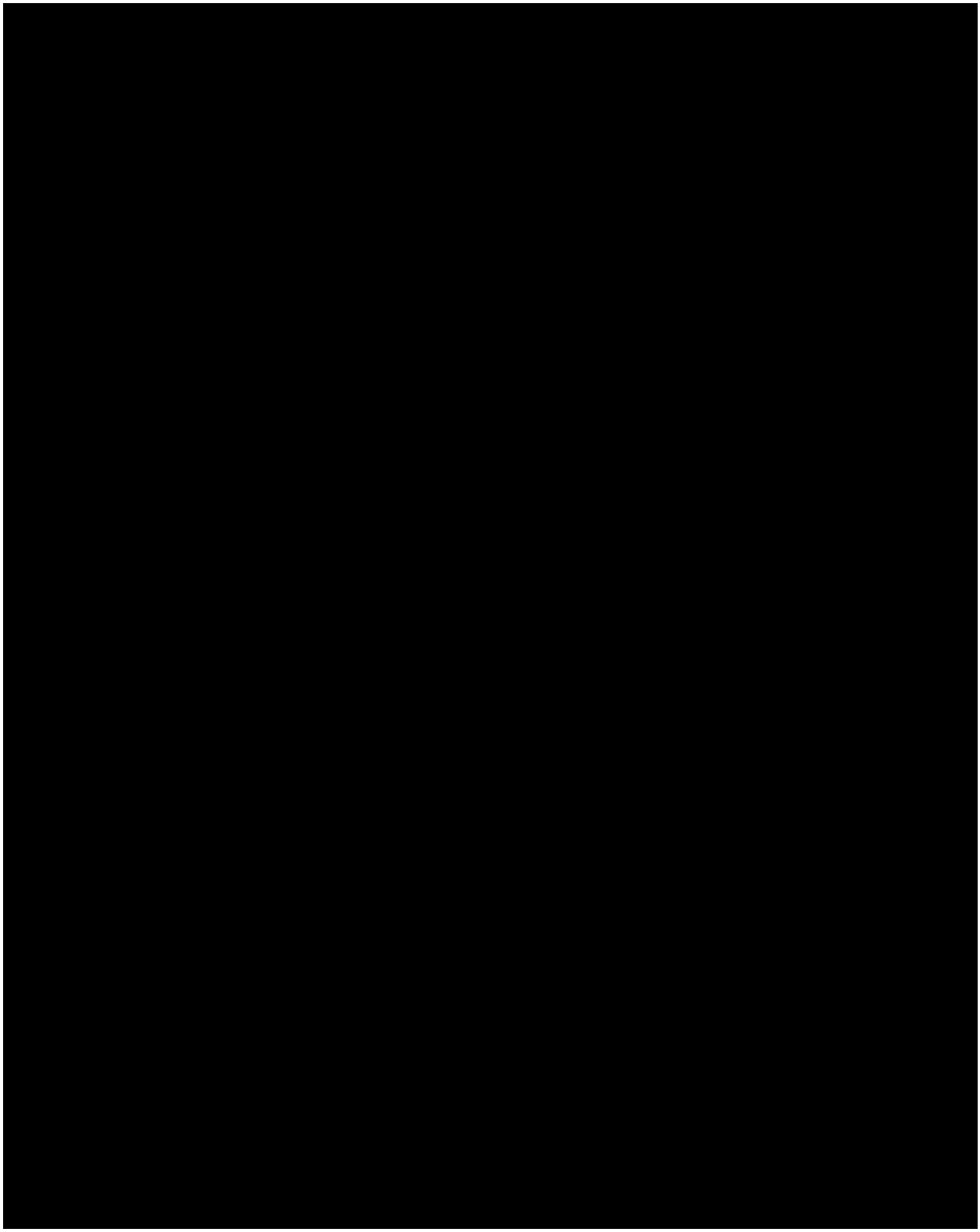
The study subject must have one eye (the same eye) meeting all the inclusion criteria (Section 4.2) and none of the exclusion criteria (Section 4.3). Study subjects will be dosed in both eyes. If both eyes are eligible at the time of randomization, the study eye will be defined as the eye with the higher pre-CAE Ora Calibra ODS score at the Baseline visit. If both eyes qualify and have the same pre-CAE Ora Calibra ODS score, then study eye will be defined as the eye with the lower anesthetized Schirmer score at the Baseline visit. If both eyes still qualify, the right eye will be designated as the study eye.

9.1.3 Missing Data

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

[redacted]





9.2 Hypotheses

The primary endpoints will be tested in a hierarchical fixed sequence in the following order.

H_{01}: The difference between study eyes treated with AR-15512 (0.003%) and study eyes treated with vehicle, in the mean change from baseline (CFB) in pre-CAE ODS VAS at Day 28 = 0.

H_{11}: The difference between study eyes treated with AR-15512 (0.003%) and study eyes treated with vehicle, in the mean CFB in pre-CAE ODS VAS at Day 28 ≠ 0.

H_{02}: The difference between study eyes treated with AR-15512 (0.003%) and study eyes treated with vehicle, in the mean CFB in pre-CAE anesthetized Schirmer score at Day 28 = 0.

H_{12}: The difference between study eyes treated with AR-15512 (0.003%) and study eyes treated with vehicle, in the mean CFB in pre-CAE anesthetized Schirmer score at Day 28 ≠ 0.

H_{03}: The difference between study eyes treated with AR-15512 (0.0014%) and study eyes treated with vehicle, in the mean CFB in pre-CAE ODS VAS at Day 28 = 0.

H_{13}: The difference between study eyes treated with AR-15512 (0.0014%) and study eyes treated with vehicle, in the mean CFB in pre-CAE ODS VAS at Day 28 ≠ 0.

H_{04}: The difference between study eyes treated with AR-15512 (0.0014%) and study eyes treated with vehicle, in the mean CFB in pre-CAE anesthetized Schirmer score at Day 28 = 0.

H_{14}: The difference between study eyes treated with AR-15512 (0.0014%) and study eyes treated with vehicle, in the mean CFB in pre-CAE anesthetized Schirmer score at Day 28 ≠ 0.

Hierarchical fixed sequence testing will be employed to maintain the type I error rate. The primary analyses will first test the difference in the mean CFB in pre-CAE ODS VAS between treatments at Day 28, H_{01}. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of AR-15512 (0.003%), then the trial will be considered a success; AR-15512 (0.003%) will be declared to be superior to vehicle in the mean CFB in pre-CAE ODS VAS at Day 28; and the difference in the mean CFB in pre-CAE anesthetized Schirmer score between treatments at Day 28, H_{02}, will be tested at the two-sided alpha = 0.05 level.

If in addition to a statistically significant test of the difference in the mean CFB in pre-CAE ODS VAS at Day 28 in favor of AR-15512 (0.003%), the test of the difference in the mean CFB in pre-CAE anesthetized Schirmer score at Day 28 is also statistically significant in favor of AR-15512 (0.003%), then AR-15512 (0.003%) will be declared to be superior to vehicle in both the mean CFB in pre-CAE ODS VAS and the mean CFB in pre-CAE anesthetized Schirmer at Day 28.

If H_{01} and H_{02} are both rejected in favor of AR-15512 (0.003%), then H_{03} and H_{04} will be tested in a similar hierarchical fashion using a two-sided alpha = 0.05.

If H_{03} and H_{04} are both rejected in favor of AR-15512 (0.0014%), then the secondary endpoints will be tested between AR-15512 0.003% and vehicle and between AR-15512

0.0014% and vehicle adjusting for multiplicity to maintain an overall two-sided alpha = 0.05 as detailed in the statistical analysis plan.

9.3 Determination of Sample Size

One hundred and eight (108) ITT population subjects (study eyes) per treatment group yields 90% power to reject H_{01} in favor of H_{11} and H_{03} in favor of H_{13} and conclude superiority of AR-15512 (0.003% or 0.0014%) over vehicle in the mean CFB pre-CAE ODS VAS at Day 28, assuming a true difference (AR-15512 minus vehicle) of -8.5, a common standard deviation of 19.0, and a two-sided alpha = 0.05.

Additionally, 108 ITT population subjects (study eyes) per treatment group yields 90% power to reject H_{02} in favor of H_{12} and H_{04} in favor of H_{14} and conclude superiority of AR-15512 (0.003% or 0.0014%) over vehicle in the mean CFB in pre-CAE anesthetized Schirmer score at Day 28 assuming a true difference (AR-15512 minus vehicle) of 1.4 mm, a common standard deviation of 3.15 mm, and a two-sided alpha = 0.05.

Accounting for subject discontinuations, approximately 360 total subjects (120 per treatment arm) will be randomized assuming a dropout rate of 10%.

9.4 Analysis Populations

The following analysis population will be considered.

9.4.1 Intent-to-Treat (ITT) Population

The ITT population includes all randomized subjects. The primary efficacy analysis will be performed on the ITT population. Subjects in the ITT population will be analyzed as randomized.

9.4.2 Per Protocol (PP) Population

The PP population includes subjects in the ITT population who do not have significant protocol deviations and who complete the trial through Day 28. 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.

9.4.3 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.

9.5 Demographics and Baseline Characteristics

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

9.6 Subject Disposition

Subject disposition will be presented in terms of the numbers and percentages of subjects who completed the study and discontinued from the study. Disposition will be summarized by treatment group and for all subjects.

The number of randomized subjects in each of the analysis populations (ITT, PP, and Safety) will be displayed by treatment.

The number and percentage of subjects who prematurely discontinue from the study and the reasons for study discontinuation will be summarized by treatment group for all subjects.

9.7 Efficacy Analysis

9.7.1 Primary Efficacy Endpoint(s)

- Change from baseline in pre-CAE ODS-VAS, at Day 28
- Change from baseline in pre-CAE anesthetized Schirmer score at Day 28

9.7.2 Primary Efficacy Analyses

The primary comparisons in this trial will be between AR-15512 (0.003%) and vehicle with hierarchical analyses between AR-15512 (0.0014%) and vehicle at Day 28 in the ITT population with available data per subject [redacted]

[redacted]

The primary efficacy endpoints (e.g., CFB in pre-CAE ODS VAS and CFB pre-CAE anesthetized Schirmer score will be summarized using continuous summary statistics and analyzed separately 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]

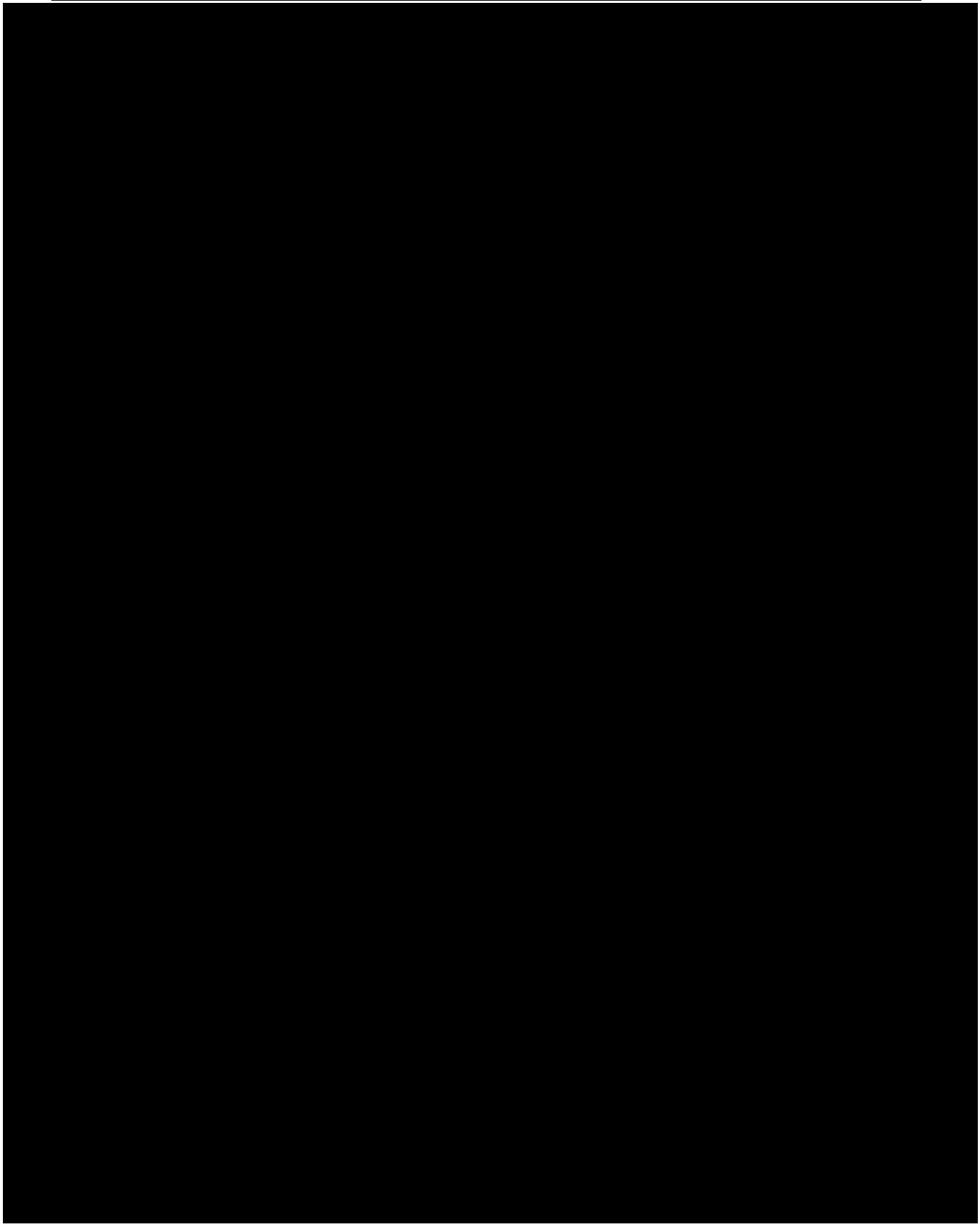
9.7.3 Secondary Efficacy Endpoint(s)

- Mean pre-CAE ODS-VAS at Day 28
- Mean Change from baseline in pre-CAE ODS-VAS at Day 84
- Mean pre-CAE ODS-VAS at Day 84
- Change from baseline in pre-CAE anesthetized Schirmer score at Day 84
- Mean pre-CAE anesthetized Schirmer score at Day 84
- Mean pre-CAE anesthetized Schirmer score at Day 28
- Change from baseline in pre-CAE Pain VAS at Day 84
- Mean pre-CAE Pain-VAS at Day 84
- Change from baseline in pre-CAE Pain-VAS at Day 28
- Mean pre-CAE Pain-VAS at Day 28
- Change from baseline in post-CAE Pain VAS at Day 84
- Mean post-CAE Pain-VAS at Day 84
- Change from baseline in post-CAE Pain VAS at Day 28
- Mean post-CAE Pain-VAS at Day 28
- Change from baseline in pre-CAE Global SANDE at Day 28
- Mean pre-CAE Global SANDE at Day 28
- Change from baseline in pre-CAE Global SANDE at Day 84
- Mean pre-CAE Global SANDE at Day 84
- Change from baseline in pre-CAE Eye Dryness (EDS)-VAS at Day 28
- Mean pre-CAE EDS-VAS at Day 28
- Change from baseline in pre-CAE Eye Dryness (EDS)-VAS at Day 84
- Mean pre-CAE EDS-VAS at Day 84

- Mean Change from baseline in pre-CAE ODS-VAS at Day 14
- Mean pre-CAE ODS-VAS at Day 14
- Change from baseline in pre-CAE Pain VAS at Day 14
- Mean pre-CAE Pain-VAS at Day 14
- Change from baseline in pre-CAE SANDE VAS at Day 14
- Mean pre-CAE Pain-SANDE at Day 14
- Change from baseline in pre-CAE EDS VAS at Day 14
- Mean pre-CAE Pain-EDS at Day 14
- Proportion of subjects with baseline anesthetized Schirmer scores ≤ 5 that achieved an anesthetized Schirmer score of ≥ 10mm at Day 84
- Proportion of subjects with baseline anesthetized Schirmer scores ≤ 5 that achieved an anesthetized Schirmer score of ≥ 10mm at Day 28

9.7.4 Secondary Efficacy Analyses

The secondary efficacy analyses will be conducted in the ITT population [redacted]



[redacted]

9.10 Safety Assessments

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of treatment-emergent adverse events (TEAEs) 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 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 AEs.

Other safety endpoints including visual acuity, slit lamp biomicroscopy, in IOP 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 Good Clinical Practice (GCP) Compliance

The proposed study is subject to all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not limited to:

- Approval of properly constituted IRBs
- Declaration of Helsinki
- US FDA Law
- International Conference on Harmonization (ICH) GCP guidelines
- Obtaining prospective informed consent

- Monitoring of the conduct of the study
- Completeness of the CRFs by the Sponsor or its designee(s)
- Appropriate record retention by the Investigator

Protocol change or amendment procedures, applicable IRB requirements, Investigator/Sponsor obligations, and study monitoring procedures are detailed in Section 10.2 through Section 10.8 of this protocol.

10.2 Investigators and Study Administrative Structure

The Principal Investigator is responsible for all site medical-related decisions. The qualified Sponsor Medical Monitor is responsible for the safe conduct of this study [redacted]

10.3 Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The ethics committee must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from or change to the protocol, without discussion with, and agreement by Aerie and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor[s], change of telephone number[s]).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

10.4 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with IRB regulations (ie, US 21 [Code of Federal Regulation] CFR Part 56.103) and GCPs. The protocol, protocol amendments, informed consent form, and all documents that will be provided to subjects will be submitted to the central and/or local IRB(s) for review and 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. Written IRB approval must adequately identify the protocol and

informed consent. A copy of the letter from the IRB indicating approval of an Investigator must be received by the Sponsor prior to conducting any study-specific procedures.
In addition to approving the protocol and an Investigator participating in the study, 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.

When the study is completed, the Investigator will provide the governing IRB with a brief final review report.

10.5 Ethical Conduct of the Study

The study will be conducted according to this clinical protocol and will be governed by the following directives and guidelines:

- US CFR, Title 21
- ICH – Consolidated Good Clinical Practices Guideline (E6)
- Standard Operating Procedures (SOPs) of the Sponsor and any vendors participating in the conduct of the study
- The ethical principles that have their origin in the Declaration of Helsinki

10.6 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 guardian prior to enrollment into the study.

All ICFs 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 or Sponsor designee 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.

10.7 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 federal laws and regulations.

Monitors, auditors and other authorized representatives of Aerie, the IRB approving this study, and government regulatory authorities (e.g., FDA and other foreign regulatory

agencies) 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 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.

10.8 Study Monitoring

Clinical research associates hired or contracted by the Sponsor 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 CRFs
- Dispensing, storage, and accountability of IP
- Source data verification
- AE and SAE reporting
- Essential documents contained within the Investigator Site File/Regulatory Binder

For source data verification (i.e., comparison of CRF entries with subject records), data will be 100% source verified.

Member(s) of the Sponsor or their designee will meet with the Investigator prior to the initiation of the study in order to assess the adequacy of the Investigator's subject population, facilities, and equipment, and to familiarize the Investigator with the protocol.

A member of the Sponsor or their designee in the role of Study Monitor will subsequently meet with the Investigator after a subject has initiated the study in order to ensure that the subjects are being properly selected, that adequate supplies for the study have been provided and that the assignment of medication is properly recorded. In addition, the Study Monitor will verify that the Investigator follows the approved protocol and all approved amendments, if any, by reviewing the Investigator's regulatory documents, source documents, Informed Consent Forms, and CRFs of study subjects.

Interim monitoring visits and telephone consultations will be done by the Study Monitor as necessary, to ensure the proper progression and documentation of the study.

The Study Monitor will meet with the Investigator when all subjects have completed the Final Visit of the study, in order to monitor the CRFs, unused study medications, and unused supplies and materials.

10.9 Case Report Forms and Study Records

The initial point of entry of study data should be the subject source documentation. The location and nature of the source documentation for all data collected in the study will be identified in the study files at the Investigator's site.

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.

Study data will be transcribed and recorded via an electronic data capture (EDC) system as electronic CRFs (eCRFs). Security and authorization procedures consistent with the EDC system must be used. At each subject visit, the appropriate eCRFs must be completed. Whenever an eCRF is used, be sure to provide all information requested including subject identification number and initials, name or number of Investigator, date(s), etc. All applicable questions should be answered and all data requested should be provided. Those areas that require a response but are not filled in correctly are considered incomplete or erroneous entries, and will have to be corrected.

Each authorized study staff member will receive a unique access account in order to use the EDC system. Access accounts will not be shared among study staff. Authorized users will make entries and/or changes to eCRFs 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.

The study records must include a copy of each Investigator's curricula vitae and medical license; completed, Form FDA 1572 or statement of Investigator; each eCRF; subject charts/source documents; Investigator's Brochure; protocol and protocol amendments; correspondence with the Sponsor and the IRB/IEC; IP storage, receipts, returns and dispensing records; Delegation of Responsibilities Log; site training records; records of site monitoring; any unmasking documentation; AE and SAE reporting; IRB/IEC approval(s); 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

A protocol deviation occurs when there is non-adherence to study procedures or schedules. Examples of deviations include common out-of-window visits or timed procedures, a missed procedure, etc. Sites will record protocol deviations in the study records. To the extent possible, sites will make their best efforts to quickly remedy deviations.

The site will contact the Sponsor for clarification of inclusion/exclusion criteria as needed prior to enrollment of a study subject. The Sponsor will document clarification requests and responses. No waivers to inclusion or exclusion criteria are allowed. If a potential subject does not meet all inclusion and/or meets an exclusion criterion during Visit 1 and Visit 2, that subject may not be enrolled in the study.

The site will notify the Sponsor or their representative and IRB within 10 days, or sooner, if required by the IRB, of becoming aware of any significant protocol deviation. Typically, significant protocol deviations include significant deviations from the inclusion and exclusion criteria that may impact the safety of a subject, concomitant medication restrictions, or any other protocol requirement that results in a significant added risk to the subject or has an impact on the quality of the data collected or the outcome of the study.

The Sponsor will review, designate, and/or approve all protocol deviations prior to database lock.

10.11 Access to Source Documentation

Monitors, auditors, and other authorized representatives of the Sponsor, the governing IRB(s)/IEC(s), the FDA, the Department of Health and Human Services (DHHS), other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the 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

After data have been entered into the study EDC system database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and the Sponsor for resolution. Where required, the Investigator will be asked for supplementary information through a query. The study EDC system 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.

Once the eCRFs are monitored in the EDC system, the data management CRO and the Sponsor will further check the eCRFs for completeness and plausibility of the data. The data management CRO will use quality systems in order to verify accurate and complete data entry, including additional checks of the data once entered in a database (e.g., range checks, cross checks, and other edit checks).

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH and US FDA guidelines for the handling and analysis of data for clinical trials. Data will be checked per the data management CRO's SOPs. The database then will be locked and a biostatistician will complete the analyses of the data in accordance with the Statistical Analysis Plan.

10.13 Retention of Data

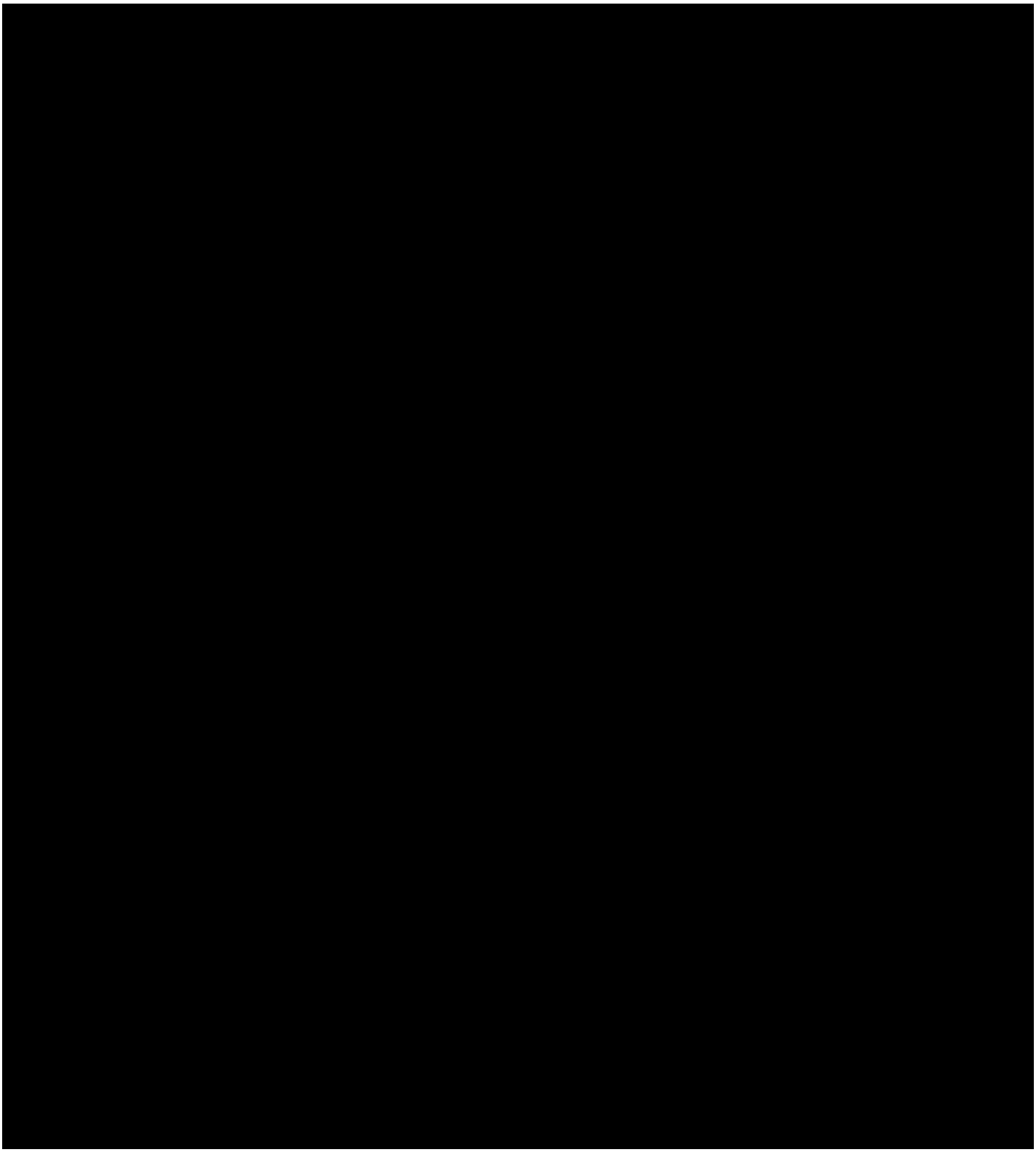
The Investigator shall retain study records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or for a period of 2 years after all investigations with the drug are discontinued and FDA has been duly notified in the circumstance that no application is to be filed or the application is not approved for such indication. The Sponsor will inform the Investigator when the study records can be destroyed.

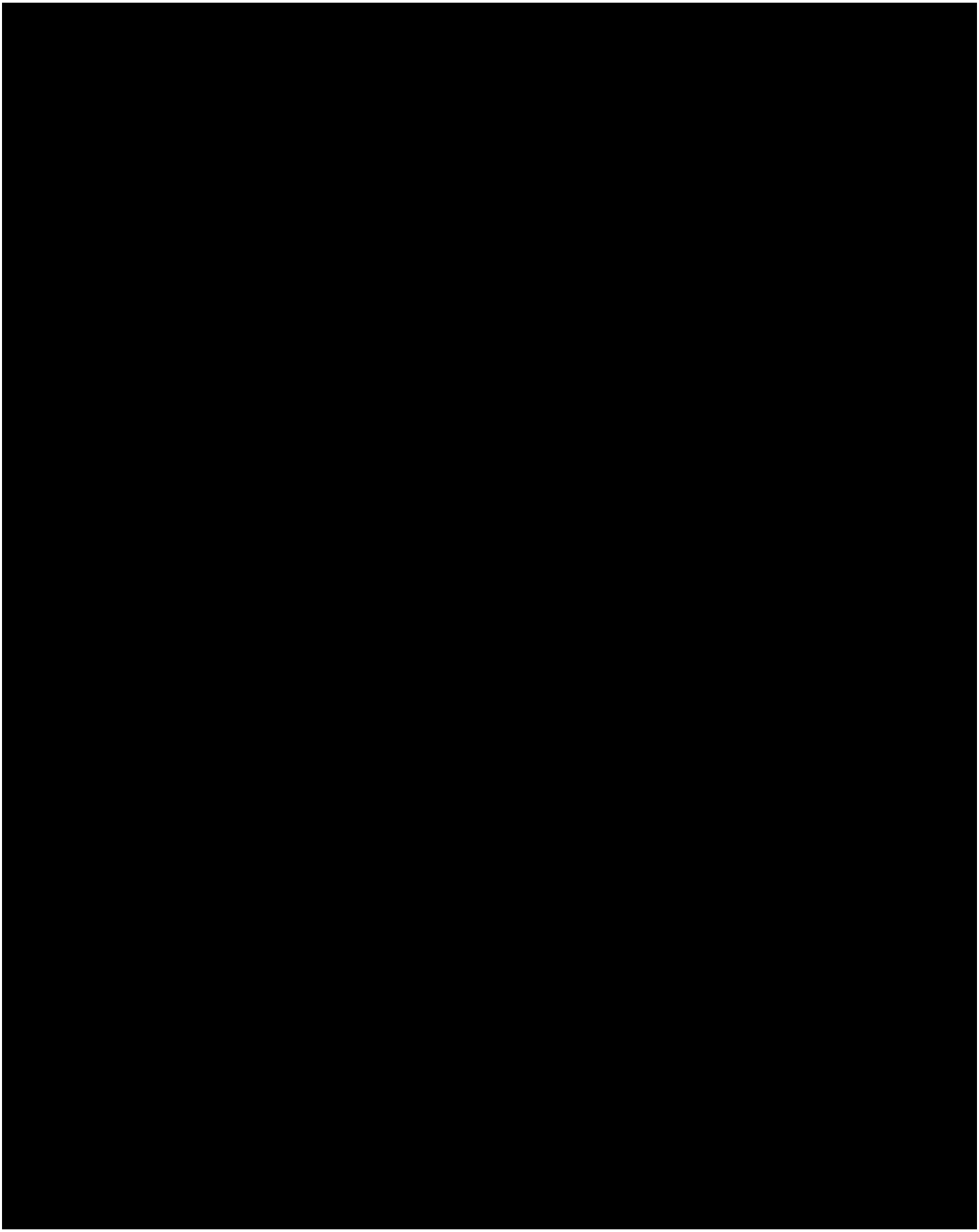
10.14 Financial Disclosure

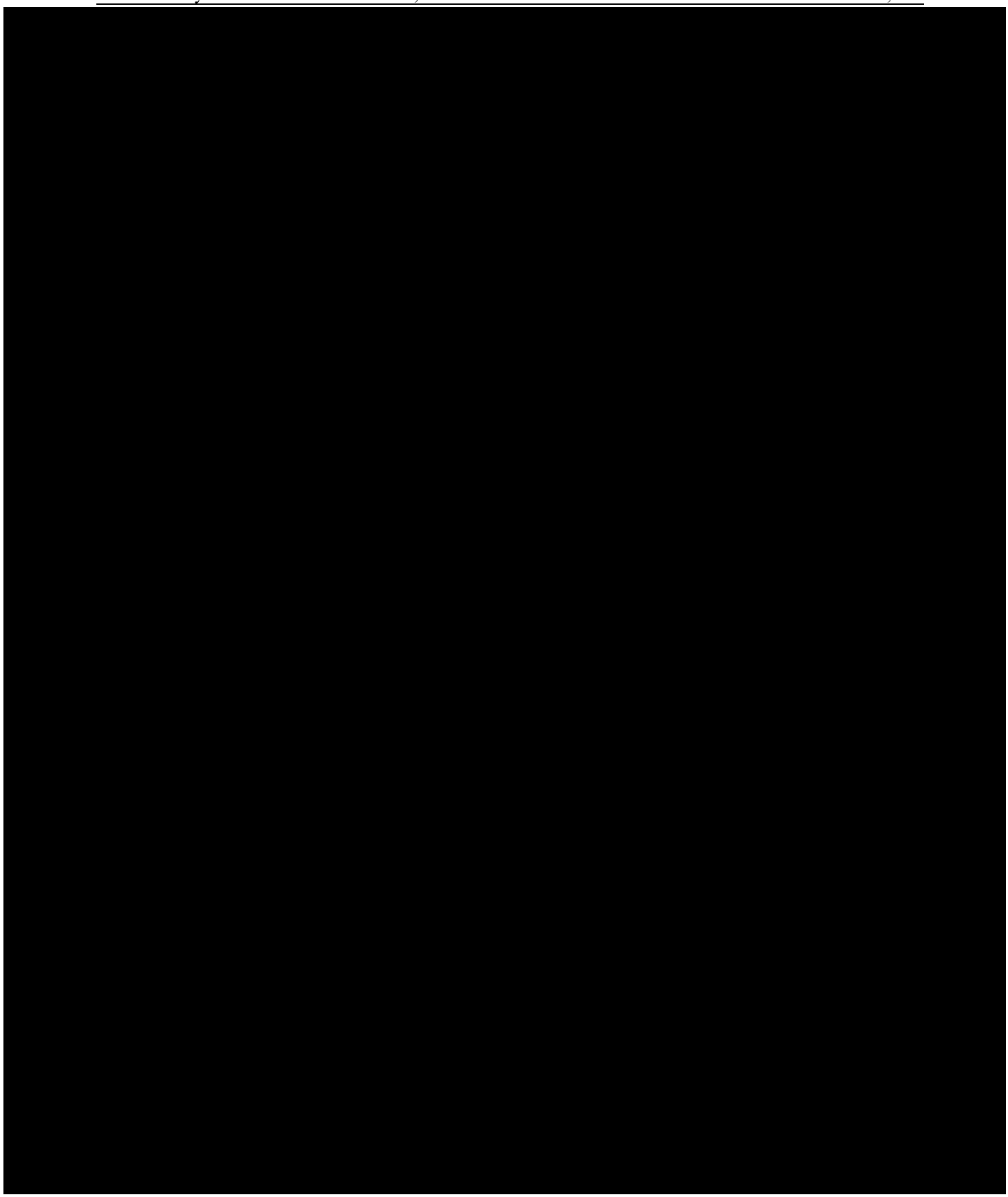
The Principal Investigator and Sub-Investigators (as listed on Form FDA 1572) will provide financial disclosure information prior to participation in the study. The Principal Investigator and any Sub-Investigators will notify the Sponsor promptly of any required revision to their financial disclosure status during the term of this study, annually, or at the end of the study (if applicable) and 1-year post-study completion. The Principal Investigator and Sub-Investigators will provide updated financial disclosure information upon the Sponsor's written request following completion of the study.

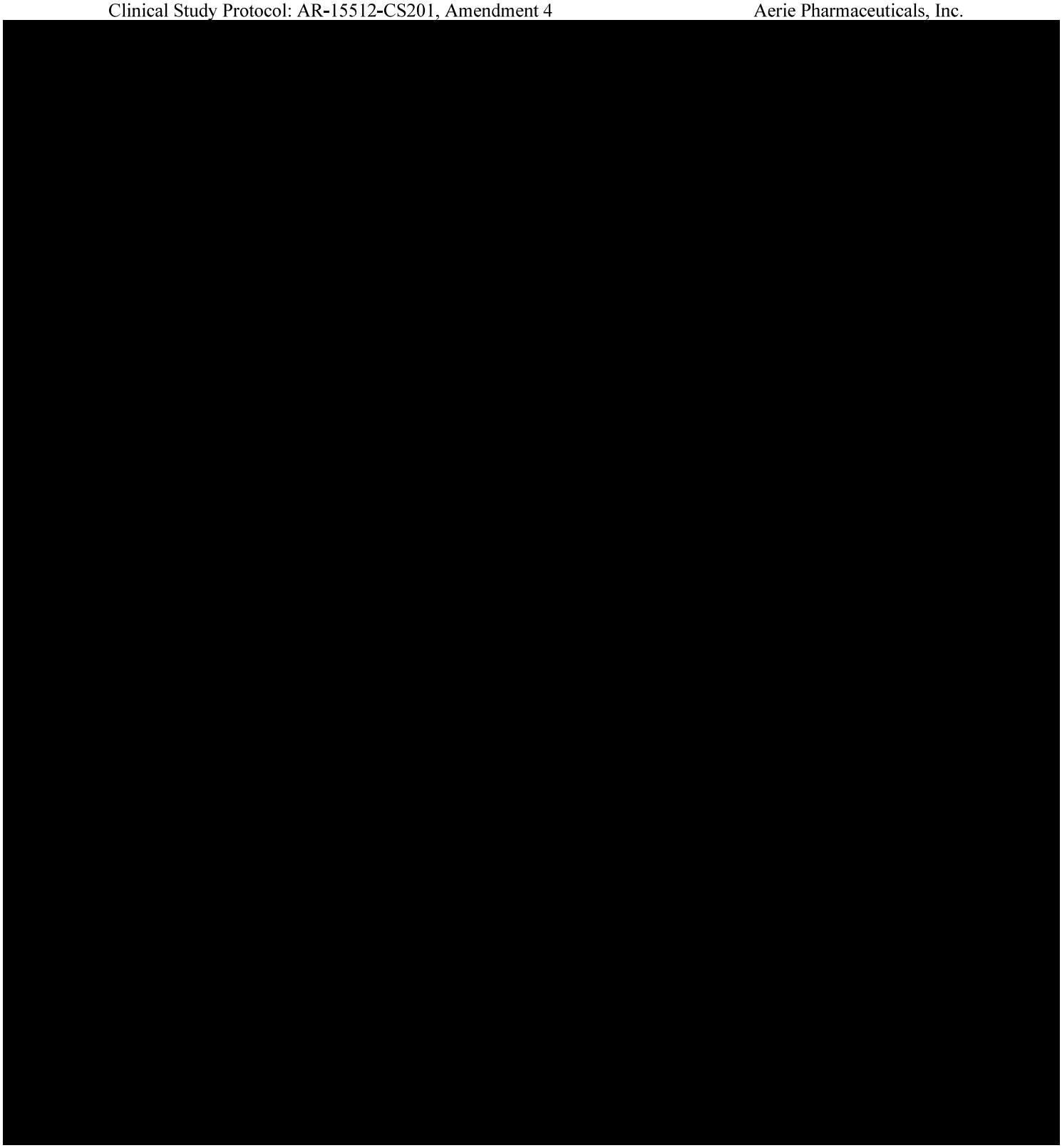
10.15 Publication and Disclosure Policy

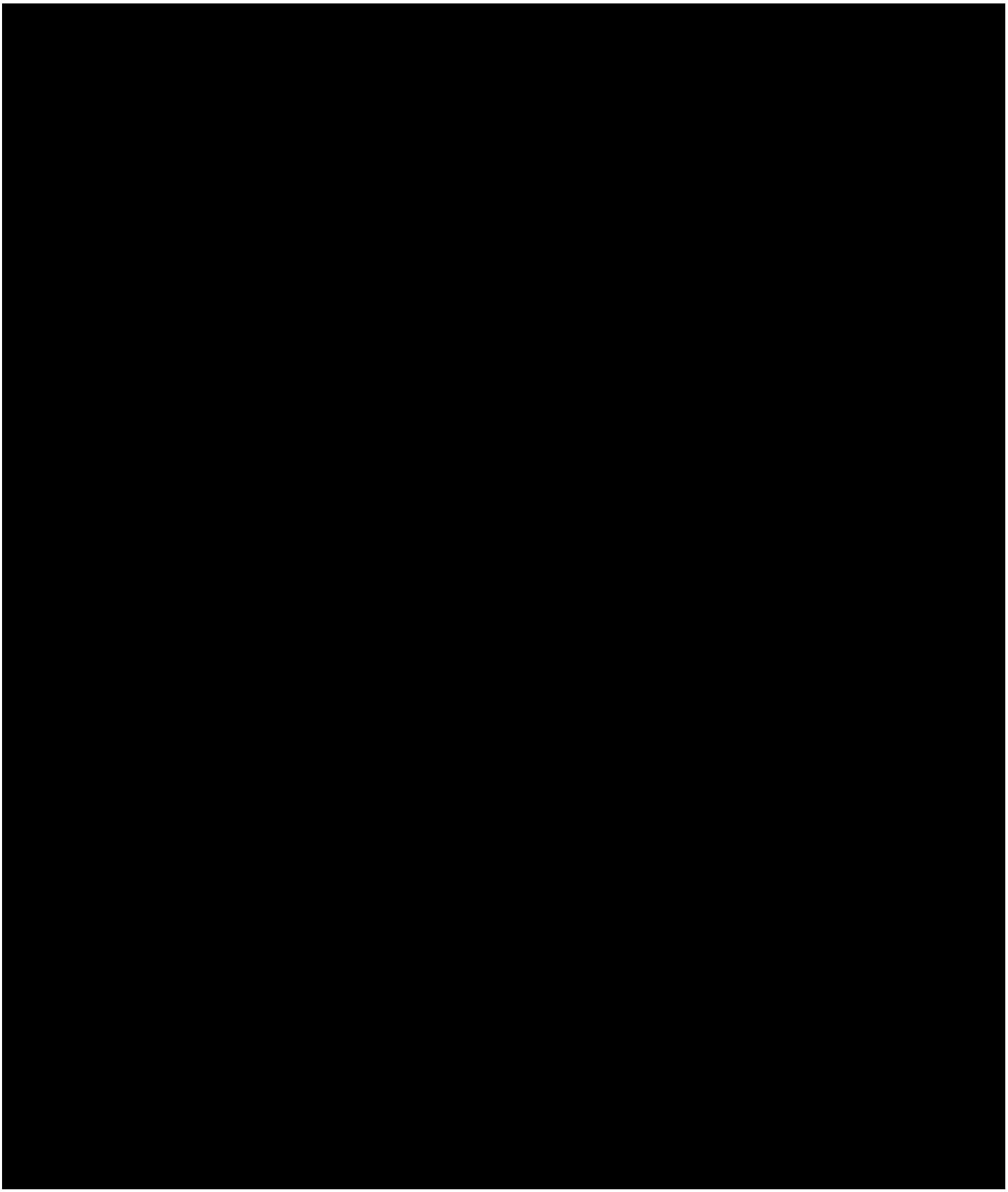
Aerie Pharmaceuticals, as the Sponsor, has proprietary interest in the study. Authorship and manuscript composition will reflect joint cooperation between multiple Investigators and sites and Aerie Pharmaceuticals personnel. For studies with multiple centers, no individual publications will be allowed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

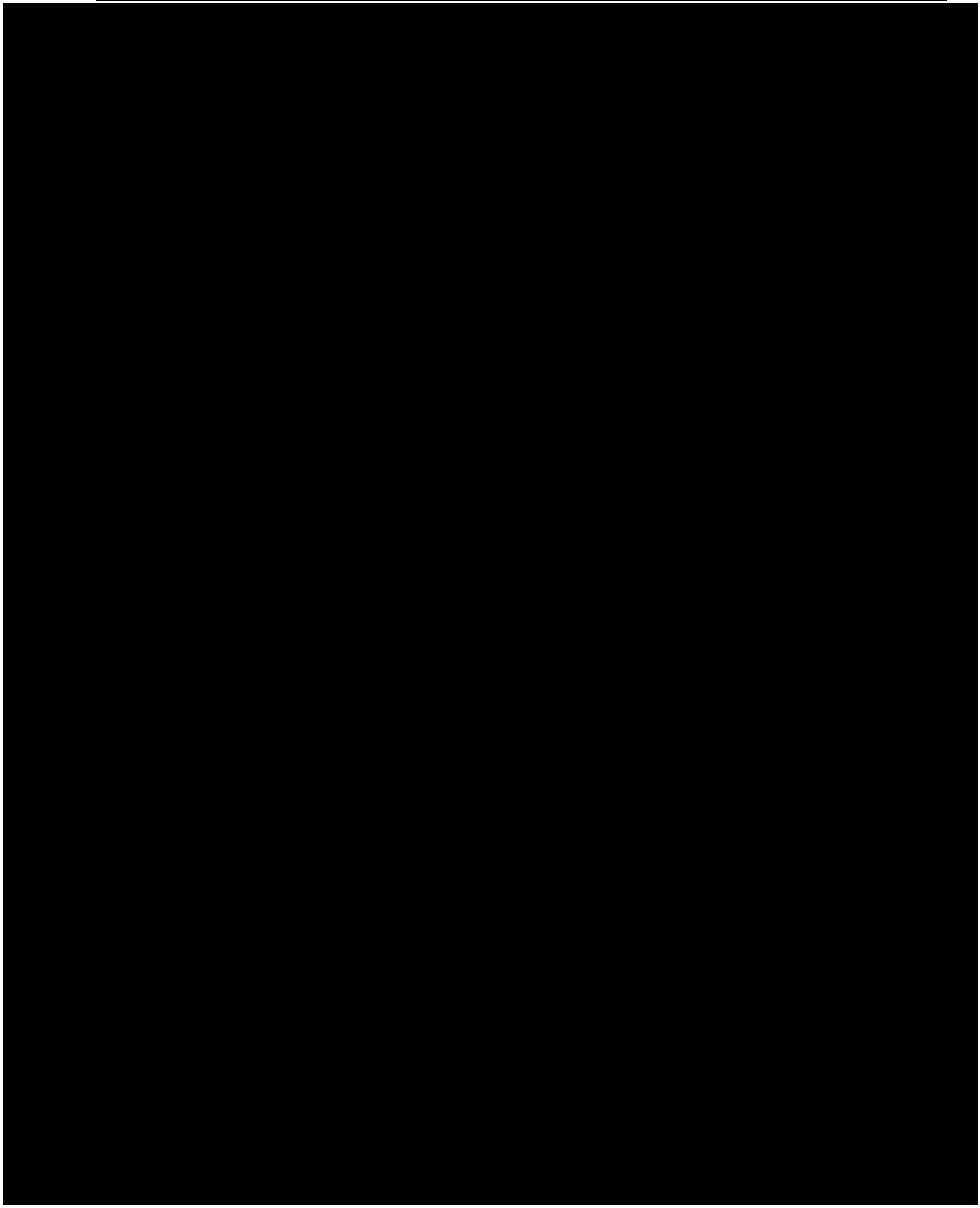


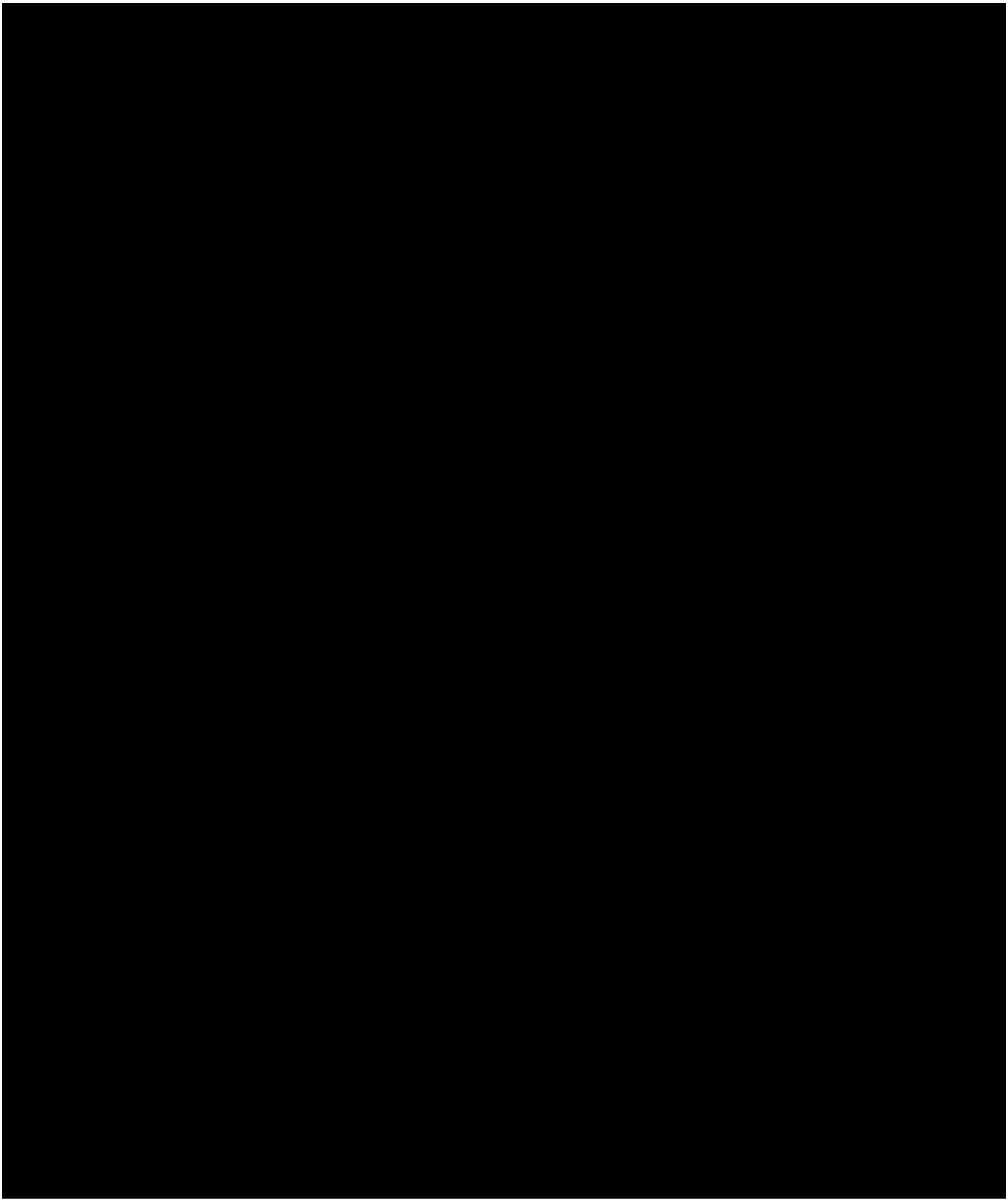


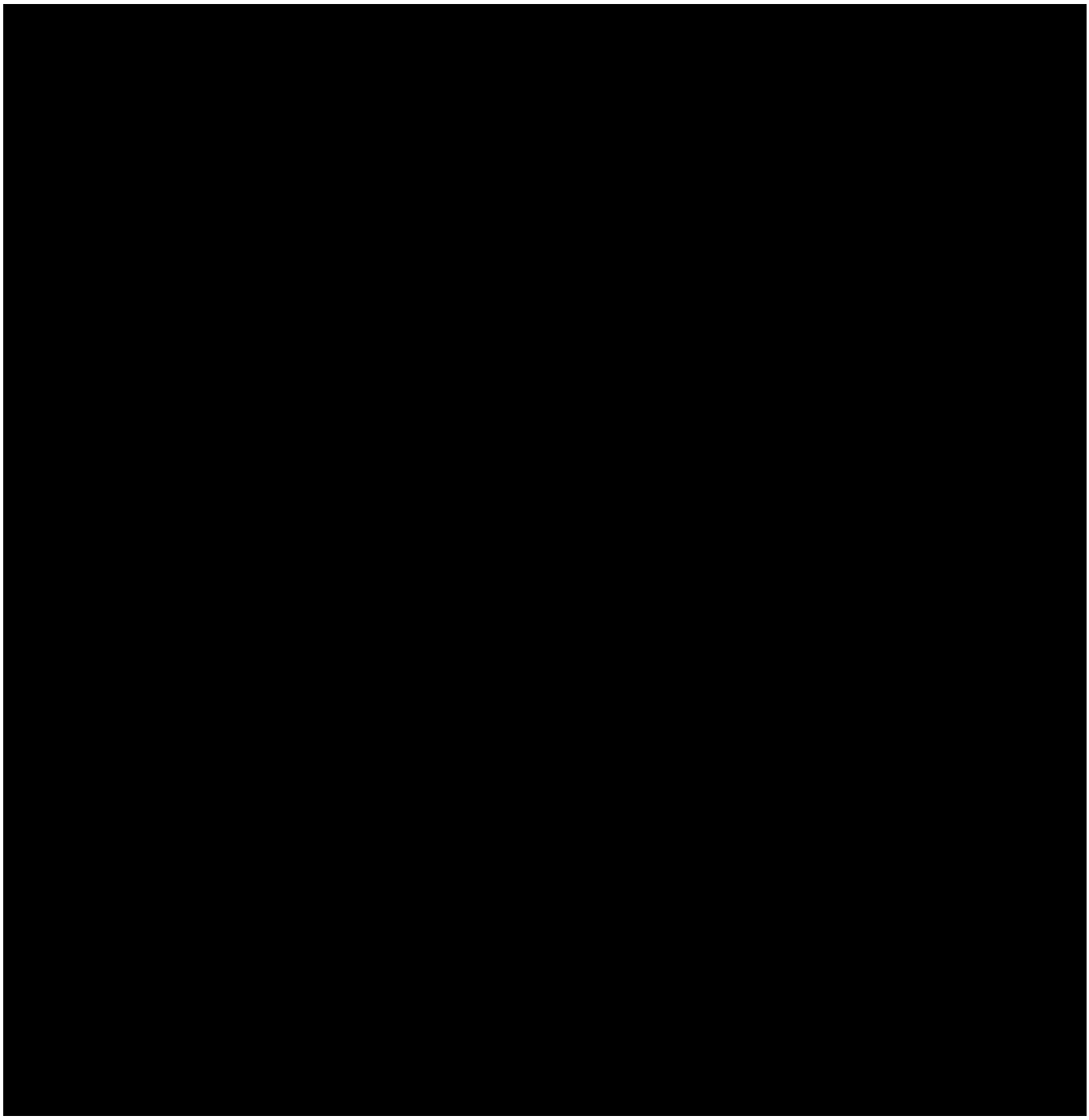


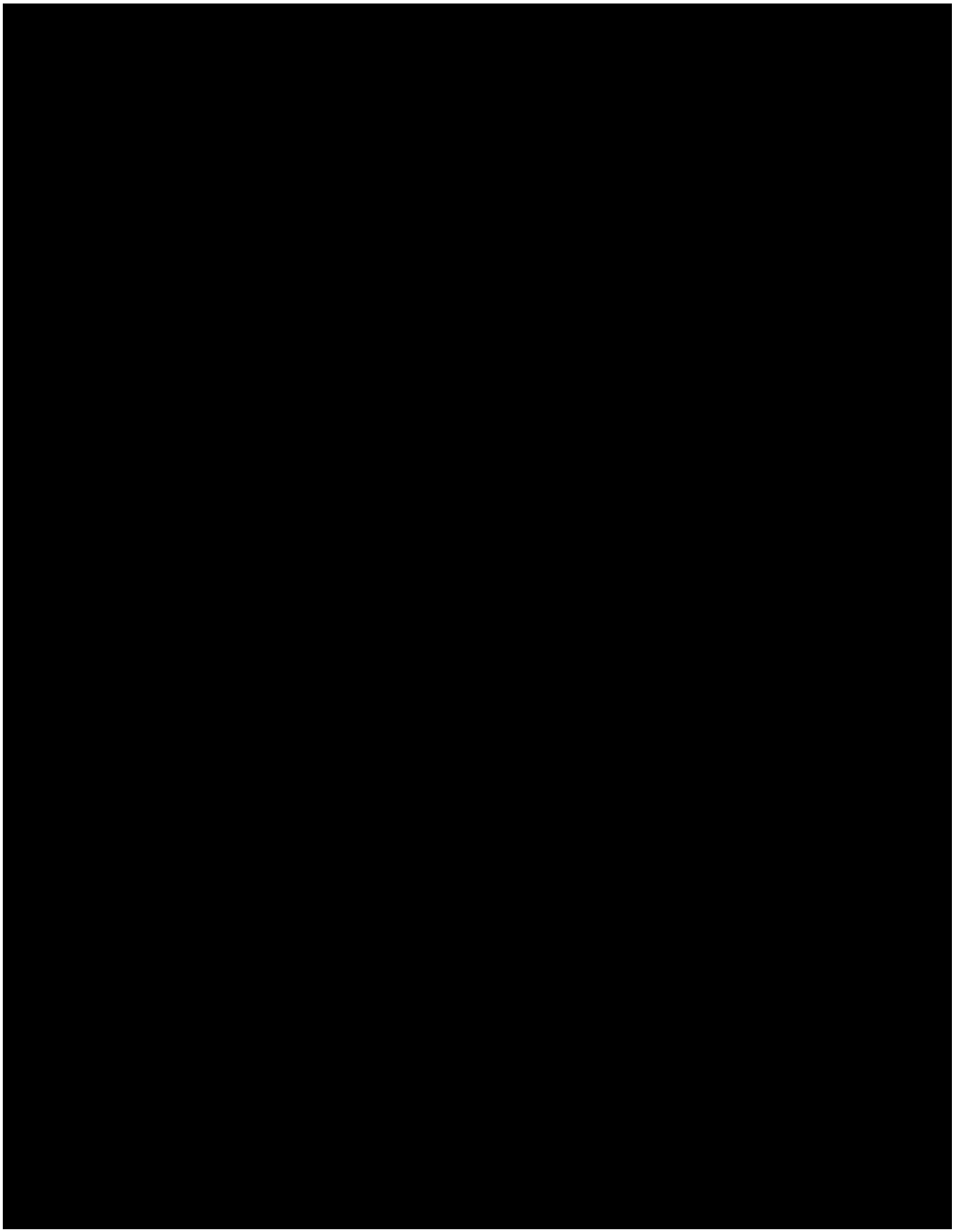


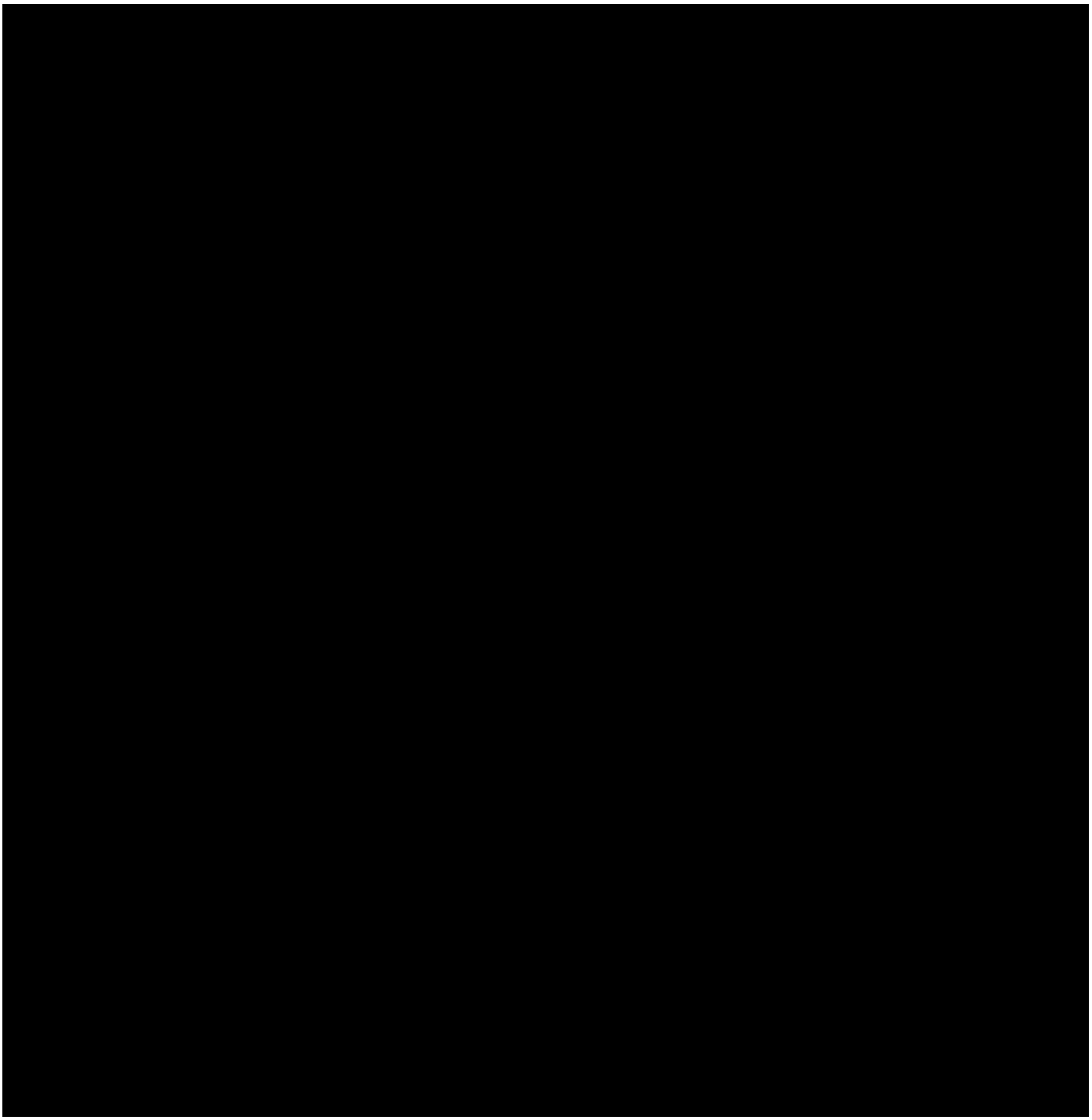












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13. APPENDICES

Appendix 1 Sponsor's Obligation

Aerie Pharmaceuticals, Inc. is committed to:

1. Complying with the local health authority regulations for the conduct of clinical research studies.

2. Informing the Investigator of any new information about the IP that may affect the subject's welfare or may influence the subject's decision to continue participation in the study.

3. Notifying the regulatory authority(ies) immediately in the event of a serious adverse experience, whether related to the use of the study medication or device or not, or the death of a subject.

4. Promptly informing the regulatory authority(ies) when the study is terminated by the Sponsor and the reason(s) for it. The IRB should also be informed promptly and provide the reason(s) for the termination by the Sponsor as specified by the applicable regulatory requirement(s).

5. Providing to the Investigator the most up-to-date editions of the Clinical Investigator's Brochure (for the IP), the protocol, Serious Adverse Experience forms, and a full set of Case Report Forms for each subject entered into the study to document the study evaluation parameters.

6. Providing study medications suitably coded and packaged for use with subjects entered into the study.

7. Providing statistical and report writing resources to complete appropriate reporting of study results.

8. Ensuring equity considerations among all Investigators in multicenter studies, including all matters of publications and meeting presentations, etc. (where applicable).

9. Prepare a Form FDA No. 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) or 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) or Sponsor's equivalent.

Appendix 2 Investigator's Obligations

The Investigator is obligated to:

1. In the event of a serious adverse experience, whether related to the use of the study medication or device or not, or the death of a subject, the Investigator is responsible for notifying the Sponsor Safety Officer immediately. The Investigator must also notify the Sponsor Representative and the Institutional Review Board (IRB) to which he/she is responsible.

2. Prior to initiating the study, sign and return to the Sponsor Representative, the relevant form (Statement of Investigator form provided by the Sponsor for studies involving non-significant risk devices, or OTC drugs; or an FDA No. 1572 is required for IND Phase I, II, III and IV studies). Each Sub-Investigator who will assist in the study is to be identified in the required form. The current curriculum vitae (signed and dated) of the principal Investigator and of each Sub-Investigator named in the Statement of Investigator form or 1572 form is to accompany the form.

3. Cooperate with the Sponsor on the preparation of an FDA Form No. 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) or 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators).

4. Obtain and submit to the Sponsor a copy of his/her IRB approval of the protocol prior to initiating the study.

5. Obtain signed informed consent from each subject or his/her legal guardian prior to acceptance of the subject into the study.

6. Read and agree to adhere to the study protocol prior to the initiation of the study. Deviations from the study protocol are not to be implemented without the prior written approval of the Sponsor and IRB, unless protection of the safety and welfare of study subjects requires prompt action. During the study, if the Investigator feels that in his/her clinical judgment, it is necessary to promptly terminate one or more subjects from the study, or 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 terminations, 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.

7. Accurately record, at the Investigator's site, all required data on each subject's electronic Case Report Form.

8. Keep accurate records of the number of study medication or device units received from the Sponsor and dispensed or administered to each subject during the study, and return any unused study medication or devices to the Sponsor at the completion of the study.

9. Before returning the study medications or devices to the Sponsor, a detailed inventory should be recorded and placed in the Investigator's file.

10. Assure that IP will be dispensed or administered only to subjects under his/her personal supervision, or under the supervision of authorized Sub-Investigators responsible to him/her.

11. Allow a representative of the Sponsor and/or representatives of health regulatory agencies to inspect all CRFs and corresponding portions of each study subject's original office, hospital, and laboratory records at mutually convenient times at regular intervals during the study and upon request after the study has been completed. The purpose of these onsite monitoring visits is to provide the Sponsor 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 CRFs, resolve any apparent discrepancies or inconsistencies in the study records, and account for all investigational supplies.

12. Provide the governing IRB with a brief (i.e., 1 to 3 pages) Investigator's summary within 90 working days of the study completion.

13. Complete the study within the time limits agreed upon with the Sponsor prior to the initiation of the study.

14. Maintenance of records:

    a. Disposition of drug: An Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the Investigator shall return the unused supplies of the drug to the Sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59.

    b. Case histories: 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 investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

    c. Record retention: An Investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor.

If for any reason the Investigator withdraws from the responsibility of maintaining the study records for the required period of time, custody of the records may be transferred to any other person who will accept responsibility for the records. The Sponsor is to be notified in writing of any such transfer.

Appendix 3 Declaration of Helsinki

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest with the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her

consent to participation at any time. The doctor should then obtain the subject's given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomforts of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, all subjects - including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic methods.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECT (NON-CLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy person or subjects for whom the experimental design is not related to the patient's illness.

3. The Investigator or the team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over consideration related to the well-being of the subject.

Appendix 4 Schedule of Visits and Procedures

Study Day	**Start of 2 Week Run-In (AR-15512 Vehicle)**		**Intervention Period (BID-OU, 1:1:1 Randomization 0.0014% AR-15512: 0.003% AR-15512: AR-15512 Vehicle)**							**Early Termination**
	Visit 1 Screening		Visit 2 Baseline		Visit 3	Visit 4		Visit 5 Study Exit		
	Day -14 (+3)[a]		Day 1		Day 14 (±2)	Day 28 (±2)		Day 84 (-5/+2)		
	Pre-CAE	Post-CAE	Pre-CAE	Post-CAE[f]	n/a	Pre-CAE	Post-CAE[f]	Pre-CAE	Post-CAE[f]	n/a
Informed consent	X									
Inclusion and exclusion criteria	X	X	X	X						
Demographics	X									
Collection of used / unused study treatment			X		X	X		X		X
Medical, ophthalmic, and surgical history	X									
Prior or concomitant medication review	X		X		X	X		X		X
AE review	X		X		X	X		X		X
Vital signs (heart rate and blood pressure)	X									
Urine pregnancy test (WOCBP only)	X		X					X		X
Symptom questionnaire (VAS) (Ocular Discomfort[b], Eye Dryness and Ocular Pain)	X	X	X	X	X	X	X	X	X	X
SANDE questionnaire (VAS)	X		X		X	X		X		X
Ora Calibra Ocular Discomfort Scale (ODS)[b]	X	X	X	X	X	X	X	X	X	X
[redacted]										
Best-corrected visual acuity	X		X		X	X		X	X	X
[redacted]										

Study Day	**Start of 2 Week Run-In (AR-15512 Vehicle)**		**Intervention Period (BID-OU, 1:1:1 Randomization 0.0014% AR-15512: 0.003% AR-15512: AR-15512 Vehicle)**							**Early Termination**
	Visit 1 Screening		Visit 2 Baseline		Visit 3	Visit 4		Visit 5 Study Exit		
	Day -14 (+3)[a]		Day 1		Day 14 (±2)	Day 28 (±2)		Day 84 (-5/+2)		
	Pre-CAE	Post-CAE	Pre-CAE	Post-CAE[f]	n/a	Pre-CAE	Post-CAE[f]	Pre-CAE	Post-CAE[f]	n/a
Slit-lamp biomicroscopy	X	X	X	X	X	X	X	X	X	X
[redacted]										
Anesthetized Schirmer test	X		X			X		X		
[redacted]										
CAE exposure	X		X[d]			X[d,e]		X[d]		
Review of qualification		X		X						
Hematology, chemistry, and urinalysis		X								
Randomization				X						
Intraocular pressure		X							X	X
Dilated fundus exam		X							X	X
Dispensing of study treatment		X		X	X		X			
[redacted]										

Study Day	**Start of 2 Week Run-In (AR-15512 Vehicle)**		**Intervention Period (BID-OU, 1:1:1 Randomization 0.0014% AR-15512: 0.003% AR-15512: AR-15512 Vehicle)**							**Early Termination**
	Visit 1 Screening		Visit 2 Baseline		Visit 3	Visit 4		Visit 5 Study Exit		
	Day -14 (+3)[a]		Day 1		Day 14 (±2)	Day 28 (±2)		Day 84 (-5/+2)		
	Pre-CAE	Post-CAE	Pre-CAE	Post-CAE[f]	n/a	Pre-CAE	Post-CAE[f]	Pre-CAE	Post-CAE[f]	n/a
[redacted]										
In office administration of study treatment		X		X	X		X			
Post-drop non-anesthetized Schirmer test				X[c]	X[c]					
Post-drop tear meniscus height by OCT at 30 sec, 1 min, 2 min and 3 min (Selected Sites) *in Study Eye Only*							X			
AE Review		X		X	X		X		X	
Study exit									X	X

a. Visit 1 should be scheduled between 11 and 14 days before Visit 2. If absolutely necessary, Visit 2 may be delayed up to 7 days (extending the run-in period to a maximum of 21 days)

[redacted]