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

STUDY ID:

AR-15512-CS201

Statistical Analysis Plan v1

August 12, 2021

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STATISTICAL ANALYSIS PLAN
Version 1.0
August 12, 2021

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

PROTOCOL NUMBER AR-15512-CS201

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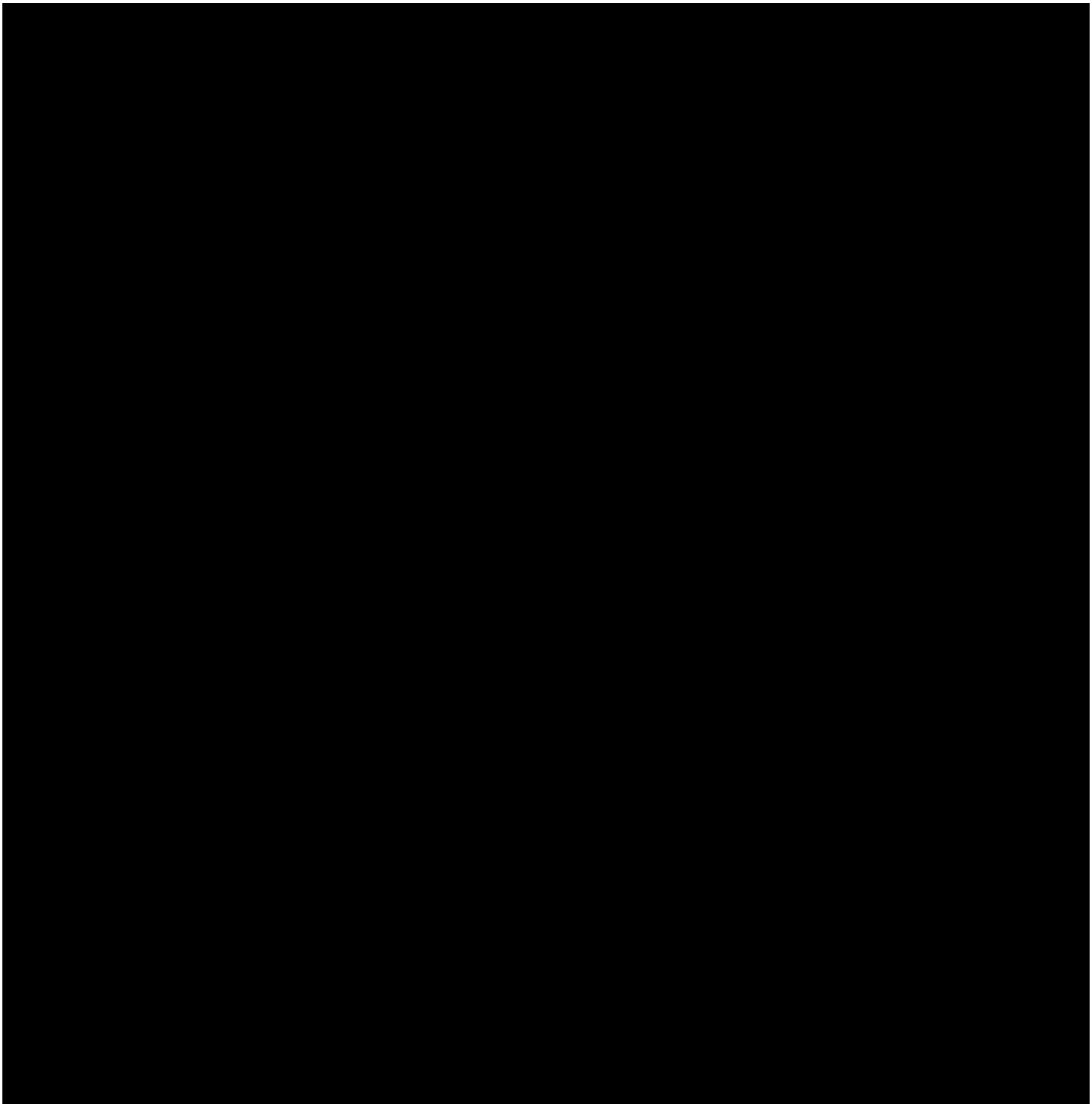

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BID	Twice Daily
CAE	Controlled Adverse Environment
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DED	Dry Eye Disease
EDS	Eye Dryness Score
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
OCT	Optical Coherence Topography
ODS	Ocular Discomfort Score
PDF	Portable Document Format
PP	Per-Protocol
PT	Preferred Term
RTF	Rich Text Format
SANDE	Symptoms Assessment in Dry Eye
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SOC	System Organ Class
[redacted]	[redacted]
TEAE	Treatment-Emergent Adverse Event
[redacted]	[redacted]
VAS	Visual Analogue Scale
WHO	World Health Organization

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is in support of the Aerie Pharmaceuticals, Inc., protocol number AR-15512-CS201 (Amendment 4 dated 2 April 2021 and, if applicable, any subsequent amendments prior to study completion), finalized before any analyses of the data. The SAP contains detailed information to aid in the performance of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR). This SAP was written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline entitled: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR.

2. PROTOCOL SUMMARY

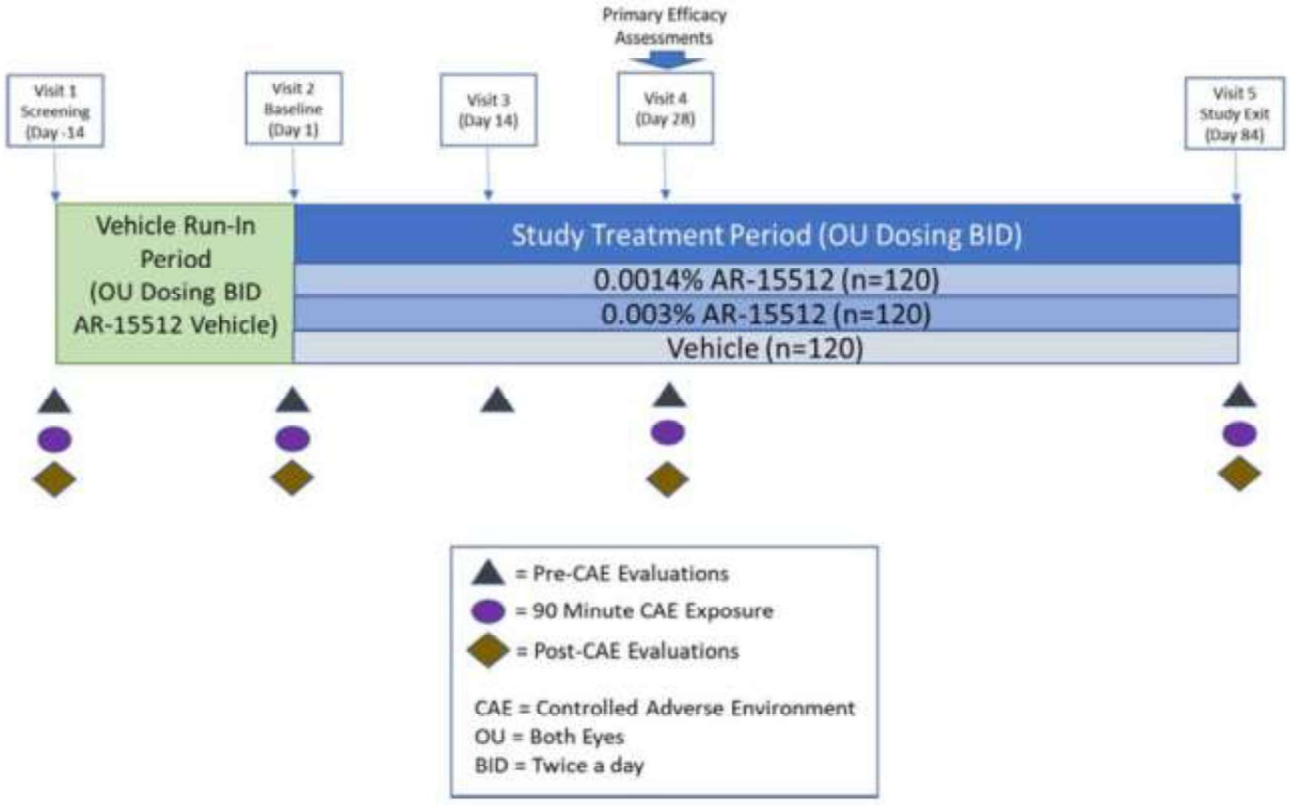
2.1 Study Objectives

The primary objective of this study is 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).

2.2 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 Controlled Adverse Environment (CAE®) at the Screening, Baseline, Day 28 and Day 84 visits. A summary of the overall study design is found in Figure 1.

Figure 1 Study Design



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 1 (Schedule of Visits and Procedures).

2.3 Study Population

This study is anticipated to enroll approximately 360 subjects with DED as defined in Protocol Sections 4.2 and 4.3 so that approximately 324 subjects complete Day 84. The anticipated dropout rate is 10%. To achieve this goal, approximately 1500 subjects may be screened.

2.4 Treatment Regimens

There will be 3 treatments in this study:

- AR-15512 ophthalmic solution, 0.0014%
- AR-15512 ophthalmic solution, 0.003%
- Vehicle (Placebo)

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). Note: If absolutely necessary, the vehicle run-in period may be extended to a maximum of 21 days per protocol.

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]

2.5 Treatment Group Assignments or Randomization

A randomization code for allocating the treatments was prepared by an independent biostatistician, who was not involved in the day-to-day conduct of the study and provided in confidence to the unmasked clinical supply manager at Aerie and the Interactive Response Technology personnel.

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% : Vehicle. The IWRS will provide the site with the specific packer number(s) for each randomized subject at the time of randomization. Sites will dispense the study treatment according to the IWRS instructions.

2.6 Sample Size Determination

One hundred and eight (108) 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 change from baseline in pre-CAE Ocular Discomfort score (ODS) Visual Analog Scale (VAS) at Day 28, assuming a true difference (AR-15512 minus vehicle) of -8.5, a common standard deviation (SD) of 19.0, and a two-sided alpha = 0.05.

Additionally, 108 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 change from baseline in pre-CAE anesthetized Schirmer score at Day 28 assuming a true difference (AR-15512 minus vehicle) of 1.4 mm, a common SD 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%.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies may be given in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

All continuous study assessments will be summarized by treatment and time point (as applicable) using descriptive statistics (n, mean, median, SD, minimum, and maximum). All categorical study assessments will be summarized by treatment and time point (as applicable) using frequency counts and percentages.

Hypothesis testing, unless otherwise indicated, will be performed at a two-sided 0.05 significance level. Where applicable, two-sided 95% confidence intervals (CIs) will be reported. All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as "<0.0001," and p-values greater than 0.9999 presented as ">0.9999."

Differences between AR-15512 and vehicle will be calculated as AR-15512 – vehicle.

Baseline is defined as the last measurement prior to the first dose of investigational product (after randomization). Change from baseline will be calculated as follow-up visit – baseline visit.

The unit of analysis for efficacy will be the study eye.

All study data will be listed by subject, treatment, and time point (as applicable). In the listings, individual subjects will be identified by a combination of site number and subject number, e.g., XXX-YYY, where XXX is the site number and YYY is the subject number.

All data analysis will be performed by Statistics & Data Corporation (SDC) after the study is completed and the database has been locked and released for un-masking. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures.

Study Eye Criteria

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

The study subject must have one eye (the same eye) meeting all the inclusion criteria (Protocol Section 4.2) and none of the exclusion criteria (Protocol 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 at the Baseline visit. If both eyes qualify and have the same pre-CAE Ora Calibra® ODS, 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.

4. ANALYSIS POPULATIONS

4.1 Intent-to-Treat Population (ITT)

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

4.2 Per-Protocol Population (PP)

The PP population is a subset of the ITT population that 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.

4.3 Safety Population

The Safety population will include all randomized subjects who have received at least one dose of the investigational product (after randomization). This population will be used to summarize safety variables. Subjects in the Safety population will be analyzed as treated.

4.4 Vehicle Run-in Population

The vehicle run-in population will include all subjects who have received at least one dose of vehicle in the run-in period.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Screen failures, subjects enrolled (i.e. subjects who entered the vehicle run-in period), subjects randomized, analysis populations, study completion, and withdrawal from the study will be summarized. The summary table will include screen failures, the number of subjects enrolled, the number of subjects randomized and included in the analysis populations by randomized treatment group for the ITT population and by actual treatment group for the PP and Safety populations. It will also include the numbers of subjects who completed and discontinued from the study. The reasons for subject discontinuation and test agent discontinuation will be summarized for the applicable subjects. Reasons for subject discontinuation will include adverse event (AE), withdrawal of consent, non-compliant, lost to follow-up, lack of efficacy, disallowed concurrent medication, investigator decision, protocol violation, death, and other.

5.2 Protocol Deviations

Protocol deviations will be evaluated for all subjects. Major protocol violations will be judged by a masked evaluation prior to the unmasking of the study treatment, for the purpose of selecting the PP population. All protocol deviations will be in a subject data listing. The number and percentage of subjects with any deviations, any major or minor deviations, related to COVID-19 will be summarized by treatment group along with the disposition data. A separate data listing for COVID-19 related protocol deviations will be provided.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the safety population and listed for all subjects. Demographic parameters will include sex assigned at birth, iris color, age in years at signing of informed consent form (ICF), race, and ethnicity. Baseline characteristics will include pre-CAE assessments scores of ODS-VAS, eye dryness (EDS) VAS, ocular pain-VAS and global SANDE as well as study eye scores for anesthetized Schirmer score [redacted]

6.2 Prior and Concomitant Medications

All prior and concomitant medications will be coded to preferred drug names and therapeutic drug class using the World Health Organization (WHO) Drug Dictionary (B3, March 2020). Prior medications are defined as medications used in the 90 days prior to first dose date of the investigational product (i.e. prior to randomization). Concomitant medications are defined as medications used on or after the first dose date of the investigational product (i.e. after randomization). Use of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 4 drug class, preferred drug name, and treatment group for the safety population. Subjects will be counted only once under each drug class and preferred term for which they have used at least one concomitant medication. All prior and concomitant medication data will also be listed.

6.3 Medical and Ocular History

All medical history and ocular history data will be presented in a by-subject listing. Medical and ocular history will be coded to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Dictionary (Version 23.0). Medical and ocular histories will be summarized for each SOC and each PT by treatment group for the safety population. Subjects will be counted only once under each SOC and PT for which they have at least one medical/ocular history.

7. MEASUREMENTS OF 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. 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.

Treatment compliance will be reported on the electronic case report form (eCRF) and listed in a subject data listing.

8. EFFICACY EVALUATION

8.1 Efficacy and Tolerability Assessments

8.1.1 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.

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

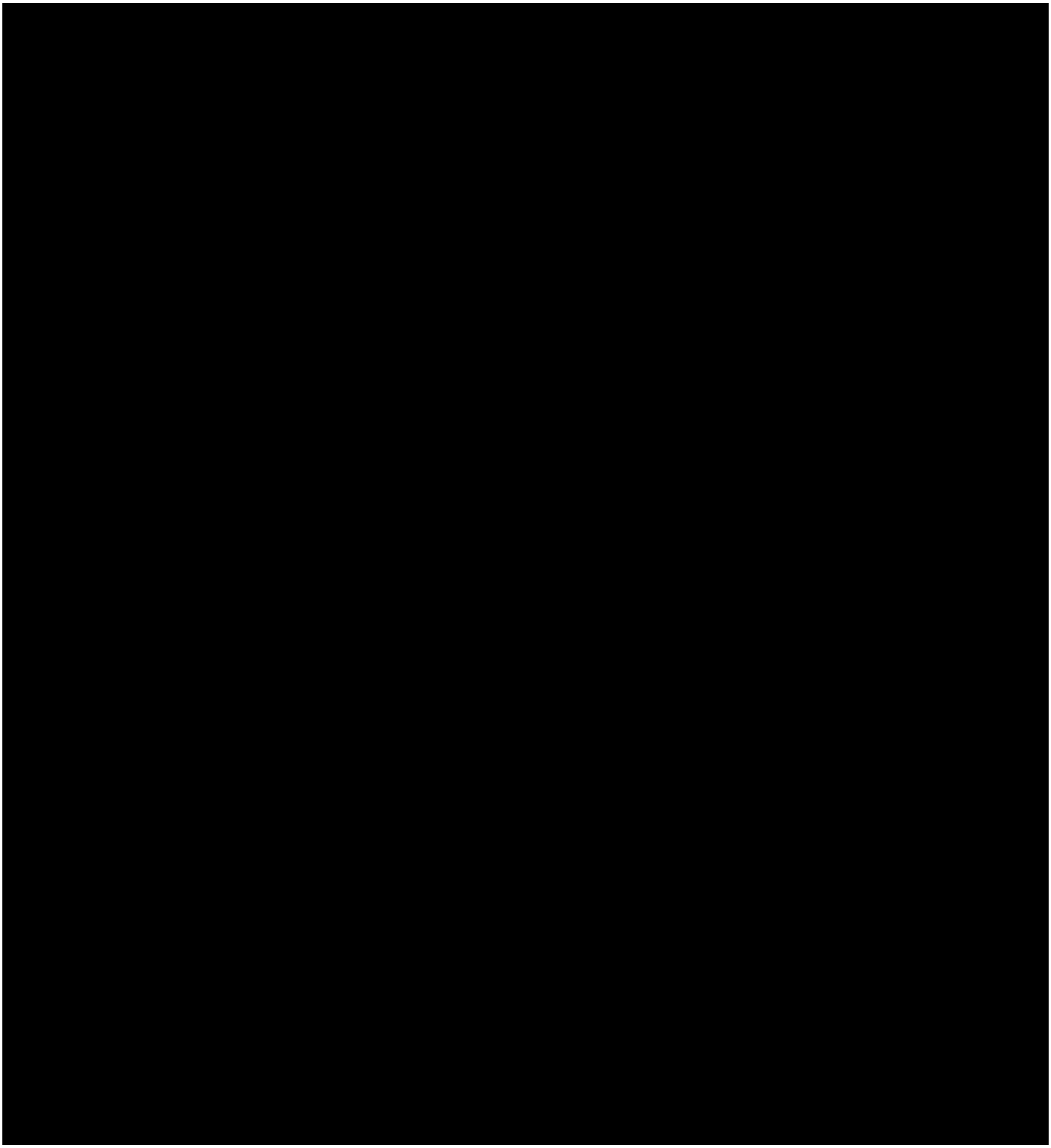
8.1.2 Symptom Assessment in Dry Eye (SANDE) Questionnaire

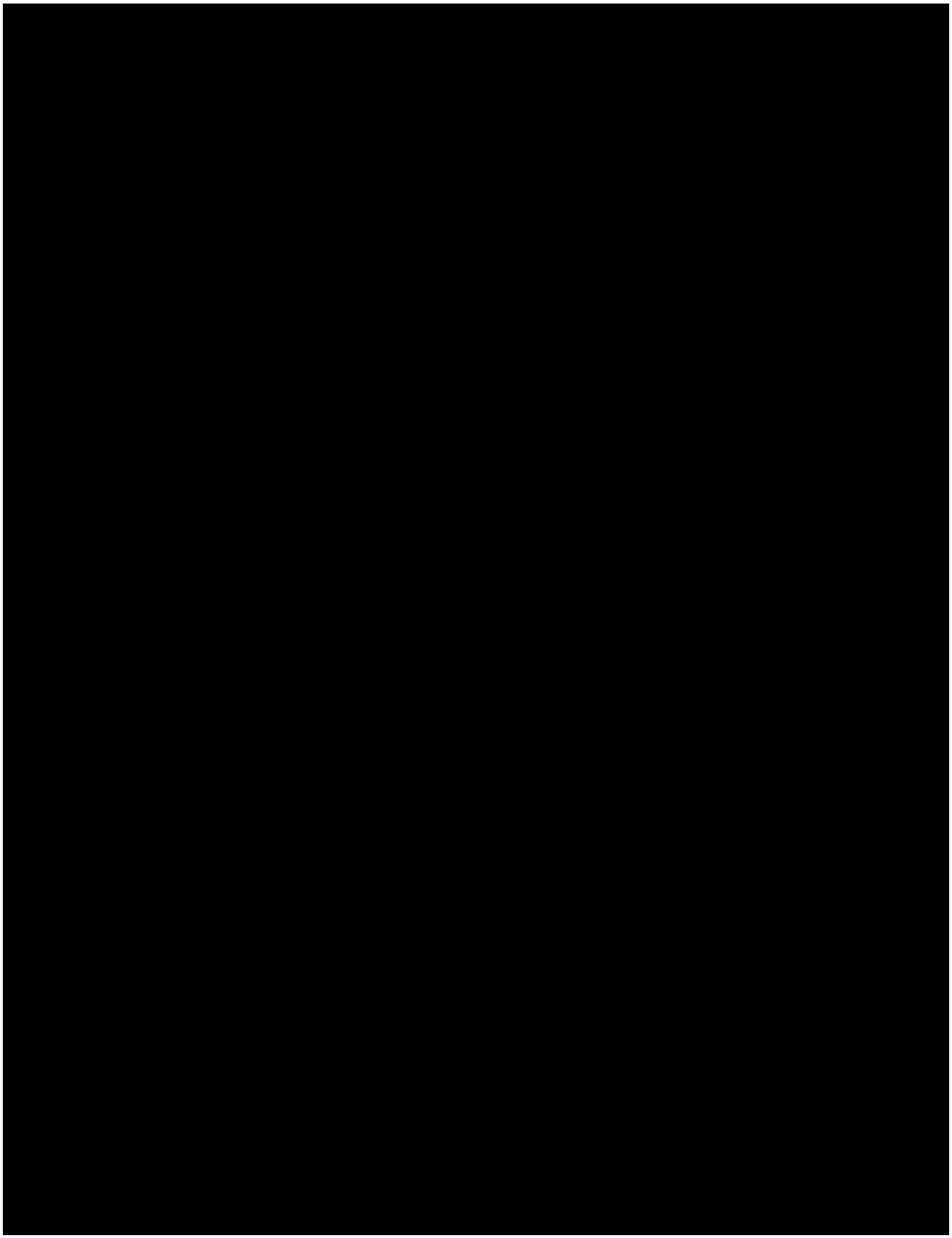
The SANDE questionnaire (Schaumberg 2007) is comprised of 2 unique VAS scales to assess the frequency and severity of DED symptoms, with each scale being 100 mm. Higher scores indicate greater frequency or severity.

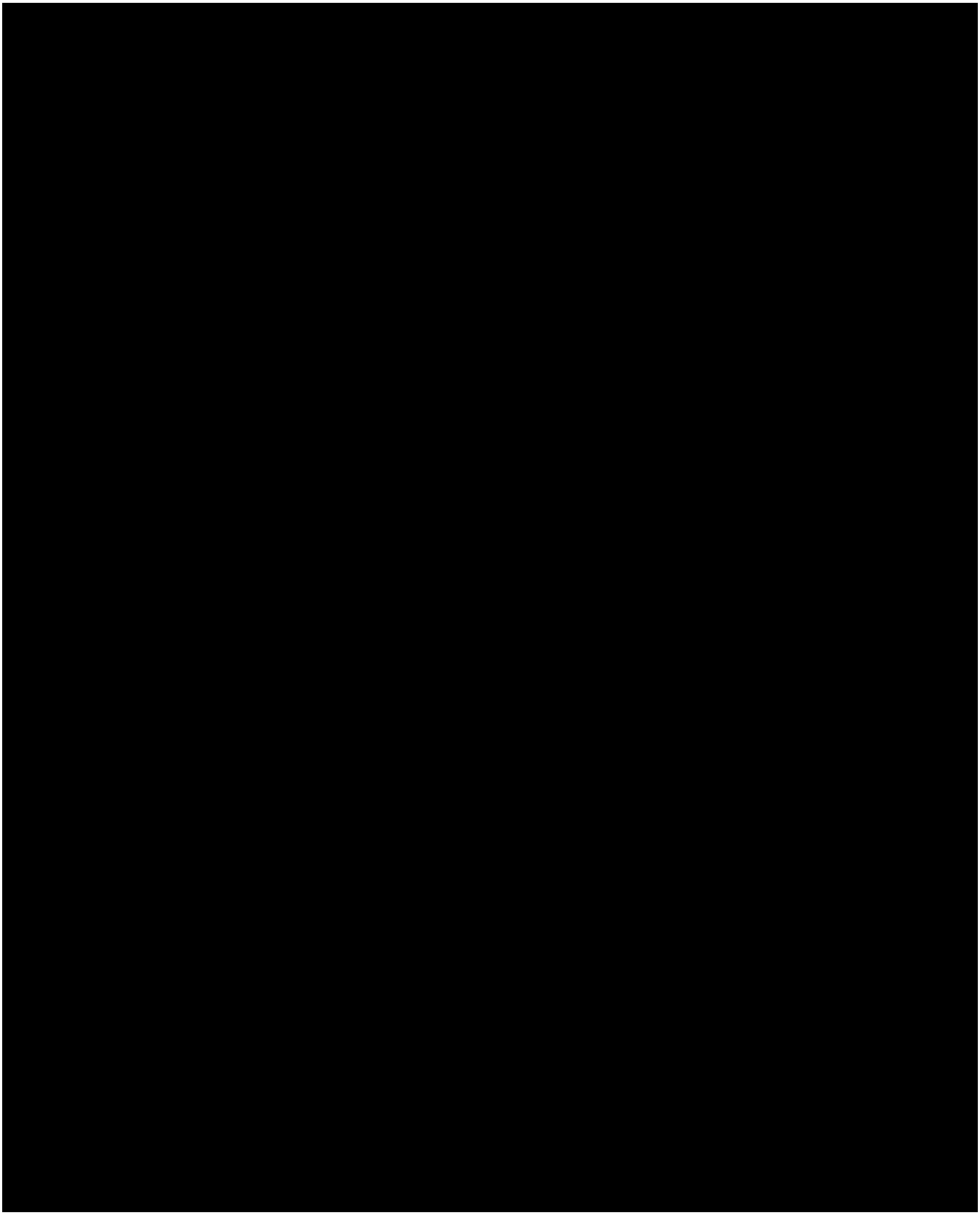
The Global SANDE score will be calculated by multiplying the frequency score by the severity score and obtaining the square root. The final value must be rounded to the nearest whole number.

8.1.6 Anesthetized Schirmer 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.





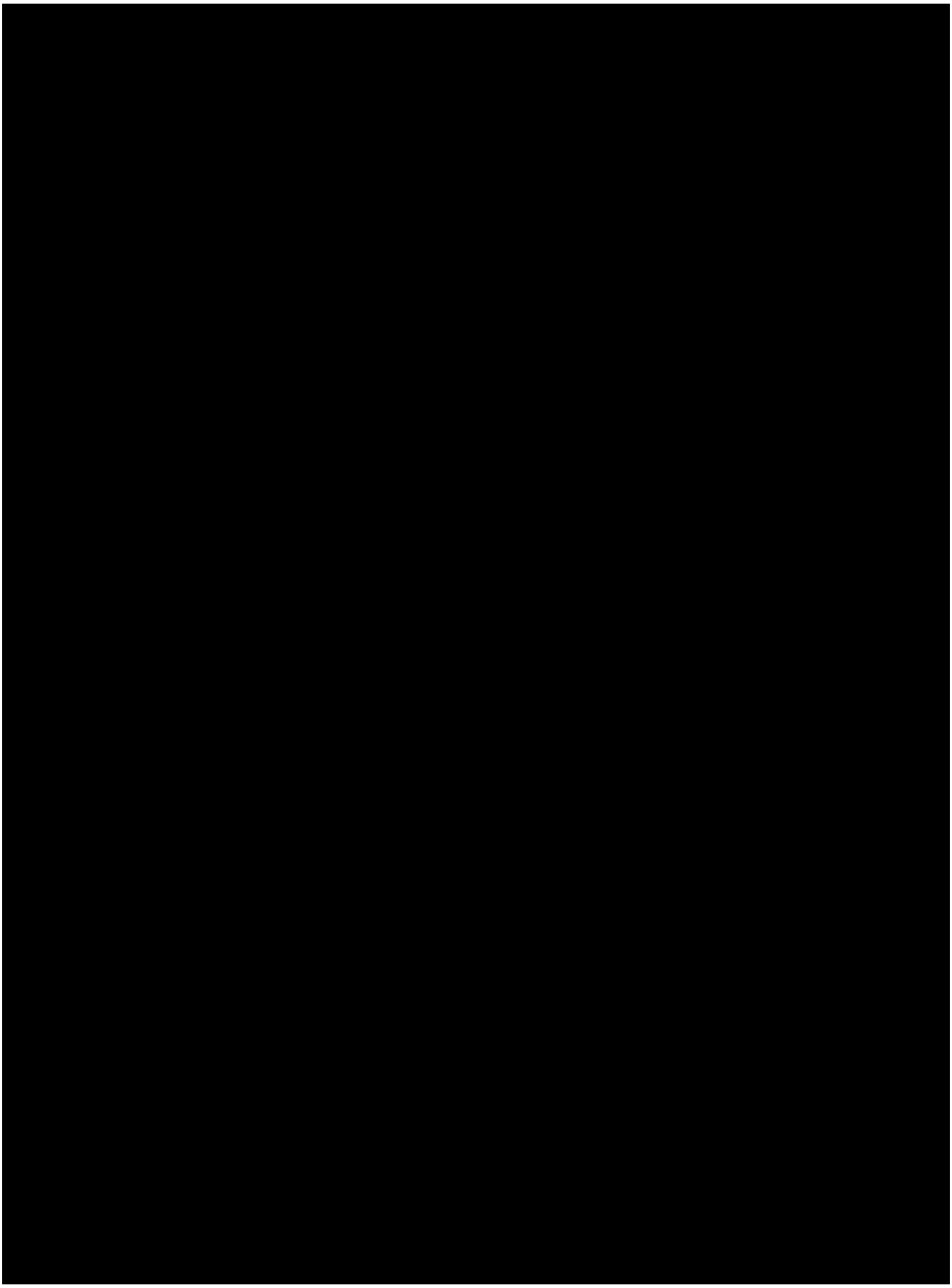


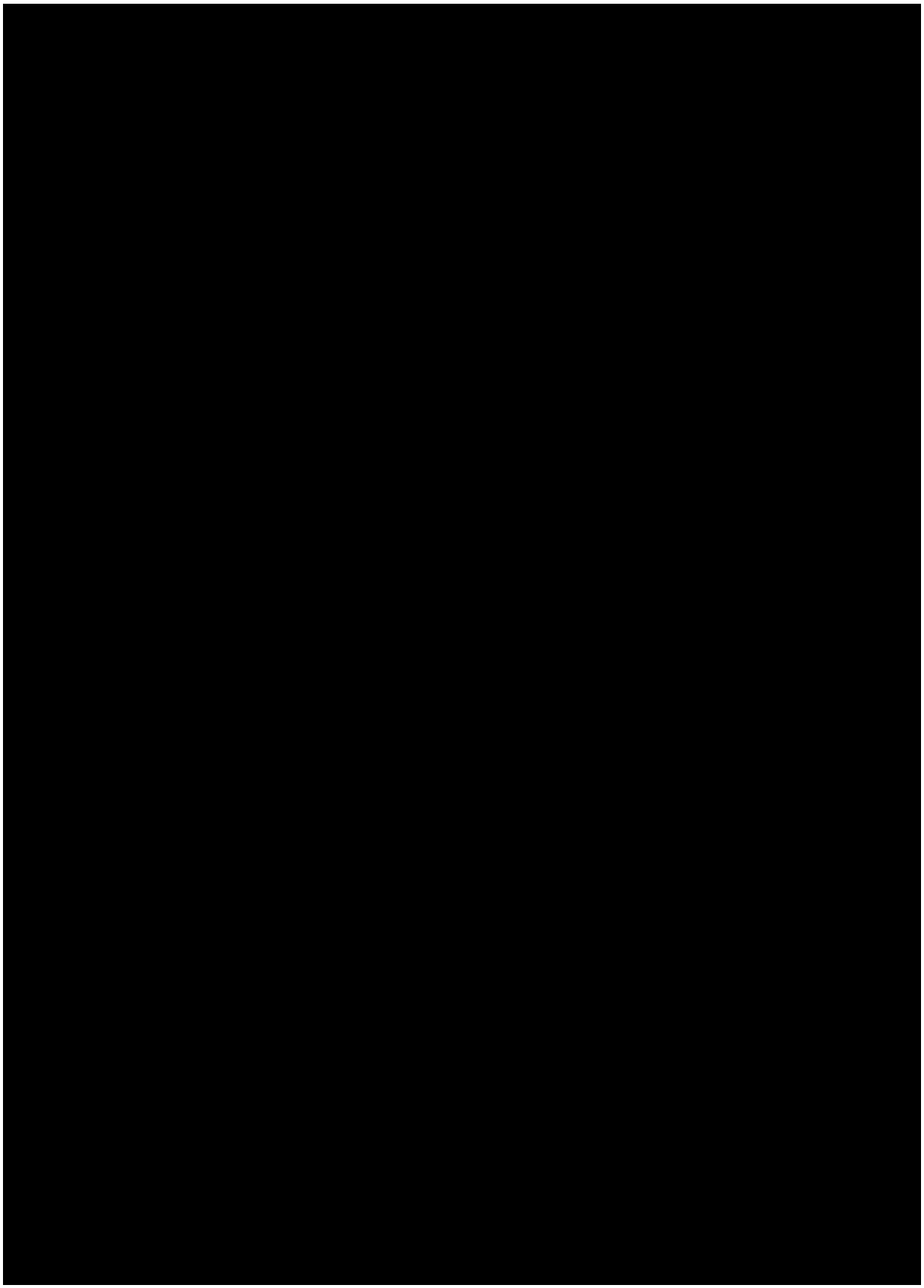
8.2 Efficacy Variables and Primary Hypotheses

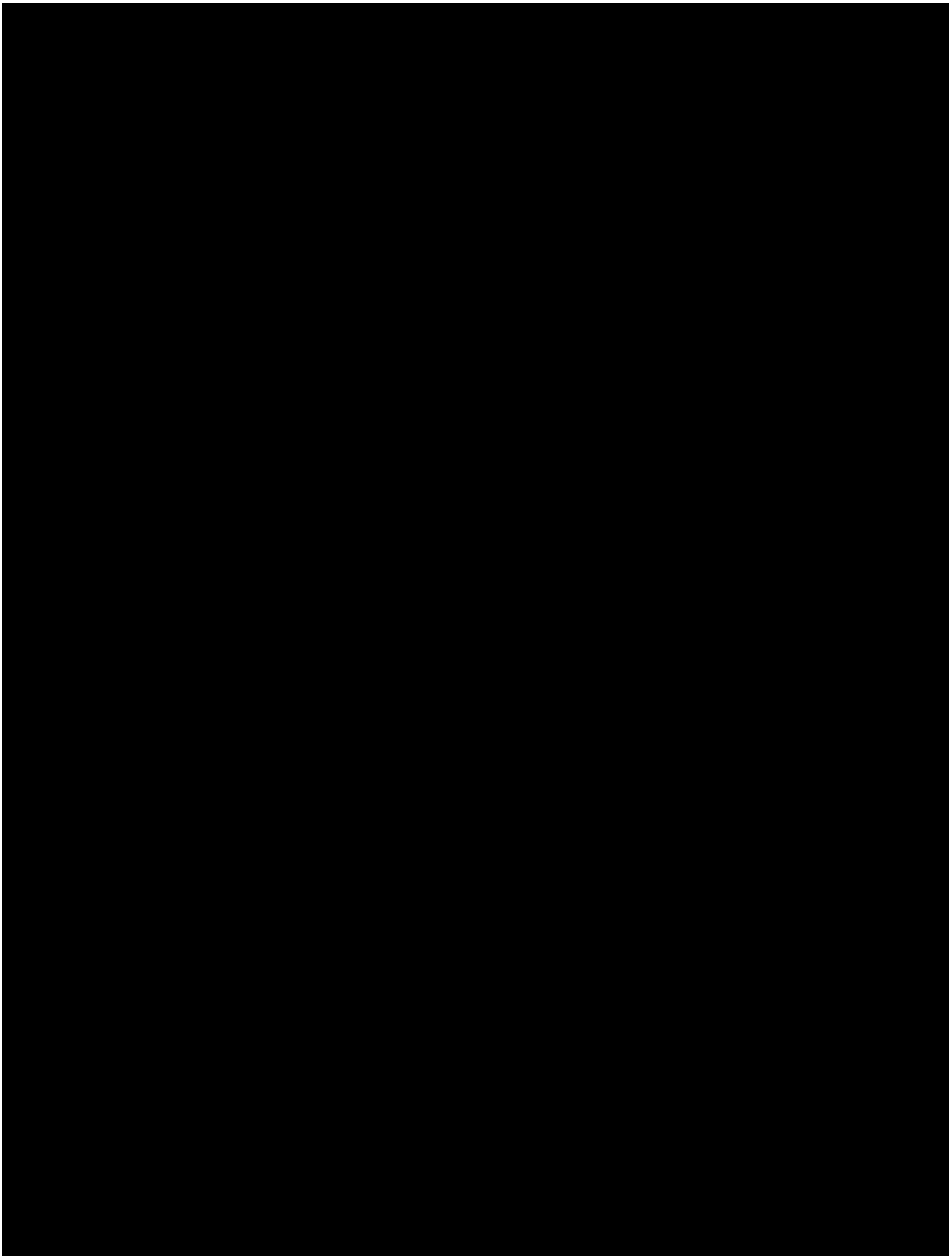
1. The co-primary efficacy endpoints will be the comparisons of AR-15512 0.003% to vehicle and AR-15512 0.014% to vehicle for:
   - Change from baseline in pre-CAE ODS-VAS at Day 28
   - Change from baseline in pre-CAE anesthetized Schirmer score at Day 28

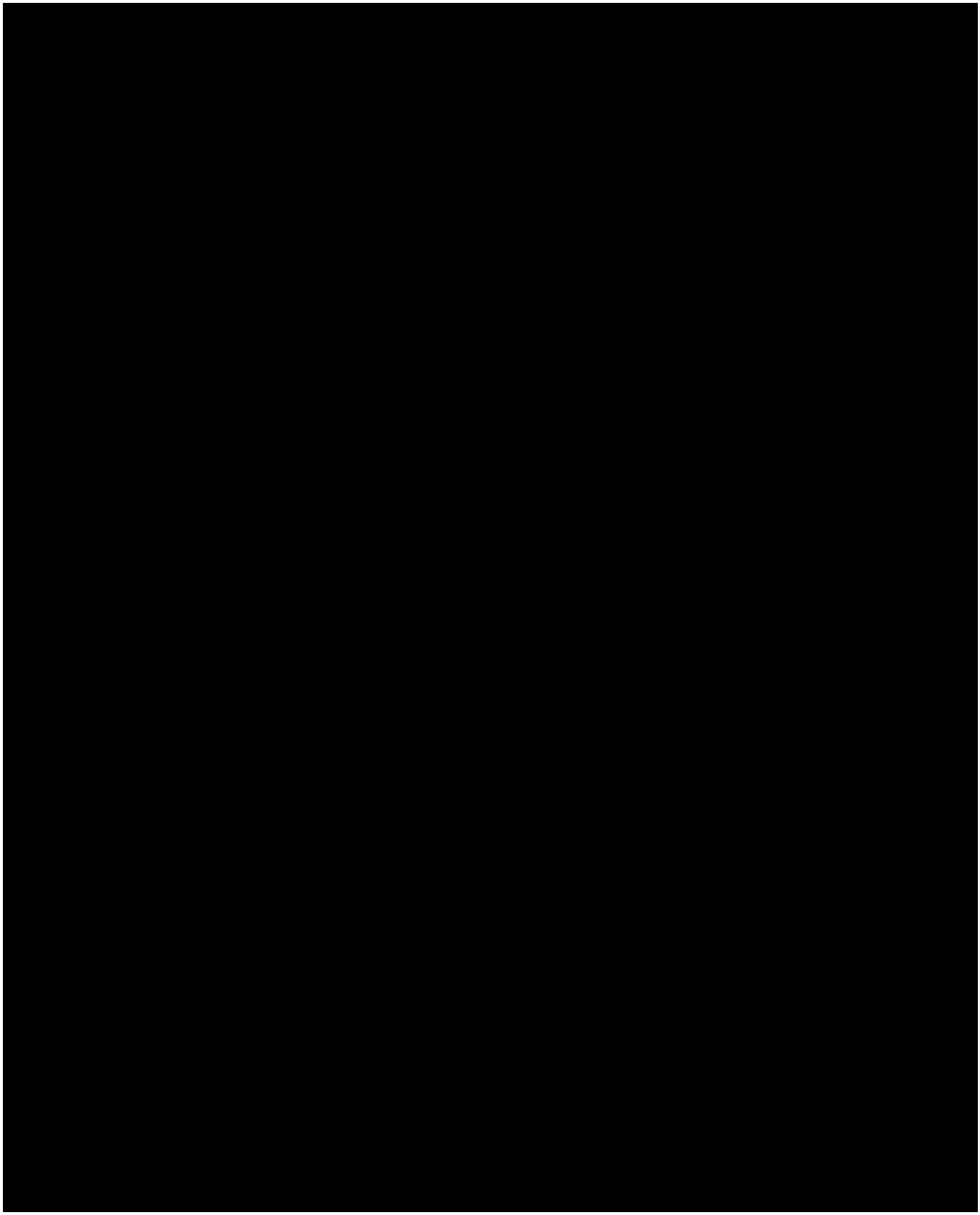
2. Secondary efficacy endpoints will include the comparisons of AR-15512 0.003% to vehicle and AR-15512 0.014% to vehicle for:
   1. Mean pre-CAE ODS-VAS at Day 28
   2. Change from baseline in pre-CAE ODS-VAS at Day 84
   3. Mean pre-CAE ODS-VAS at Day 84
   4. Change from baseline in pre-CAE anesthetized Schirmer score in study eyes at Day 84
   5. Mean pre-CAE anesthetized Schirmer score in study eyes at Day 84
   6. Mean pre-CAE anesthetized Schirmer score in study eyes at Day 28
   7. Change from baseline in pre-CAE Pain VAS at Day 84
   8. Mean pre-CAE Pain-VAS at Day 84
   9. Change from baseline in pre-CAE Pain-VAS at Day 28
   10. Mean pre-CAE Pain-VAS at Day 28

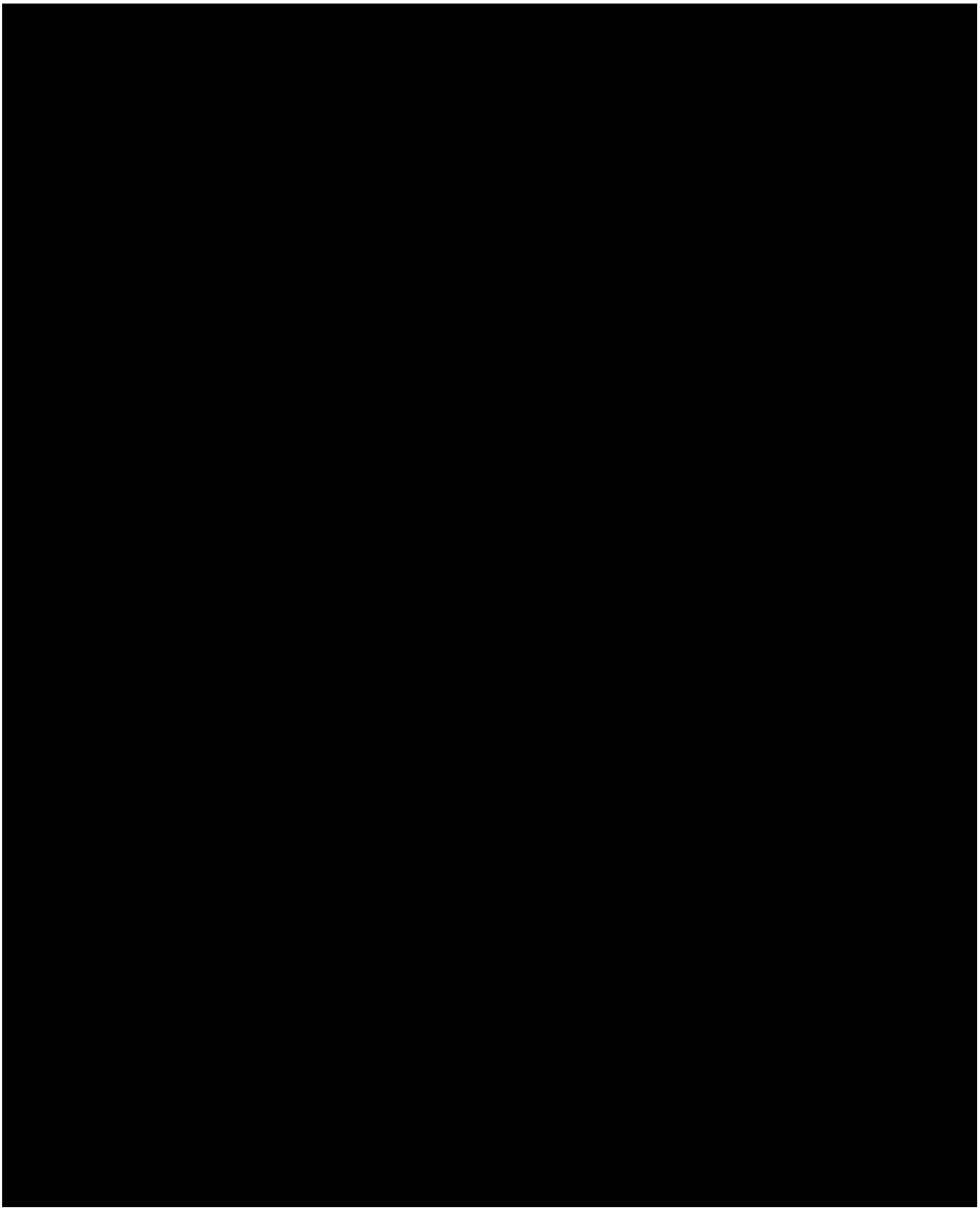
11. Change from baseline in post-CAE Pain VAS at Day 84
12. Mean post-CAE Pain-VAS at Day 84
13. Change from baseline in post-CAE Pain VAS at Day 28
14. Mean post-CAE Pain-VAS at Day 28
15. Change from baseline in pre-CAE Global SANDE at Day 28
16. Mean pre-CAE Global SANDE at Day 28
17. Change from baseline in pre-CAE Global SANDE at Day 84
18. Mean pre-CAE Global SANDE at Day 84
19. Change from baseline in pre-CAE Eye Dryness (EDS)-VAS at Day 28
20. Mean pre-CAE EDS-VAS at Day 28
21. Change from baseline in pre-CAE Eye Dryness (EDS)-VAS at Day 84
22. Mean pre-CAE EDS-VAS at Day 84
23. Change from baseline in pre-CAE ODS-VAS at Day 14
24. Change from baseline in pre-CAE Ora Calibra® ODS in study eyes at Day 28
25. Change from baseline in pre-CAE Ora Calibra® ODS in study eyes at Day 84
26. Mean pre-CAE ODS-VAS at Day 14
27. Change from baseline in pre-CAE Pain VAS at Day 14
28. Mean pre-CAE Pain-VAS at Day 14
29. Change from baseline in pre-CAE Global SANDE at Day 14
30. Mean pre-CAE Global SANDE at Day 14
31. Change from baseline in pre-CAE EDS VAS at Day 14
32. Mean pre-CAE EDS-VAS at Day 14
33. Proportion of subjects with baseline anesthetized Schirmer scores ≤ 5 that achieved an anesthetized Schirmer score of ≥ 10mm in study eyes at Day 84
34. Proportion of subjects with baseline anesthetized Schirmer scores ≤ 5 that achieved an anesthetized Schirmer score of ≥ 10mm in study eyes at Day 28
35. Proportion of subjects that achieved at least a 10 mm increase in pre-CAE anesthetized Schirmer score relative to baseline in study eyes at Day 28
36. Proportion of subjects that achieved at least a 10 mm increase in pre-CAE anesthetized Schirmer score relative to baseline in study eyes at Day 84

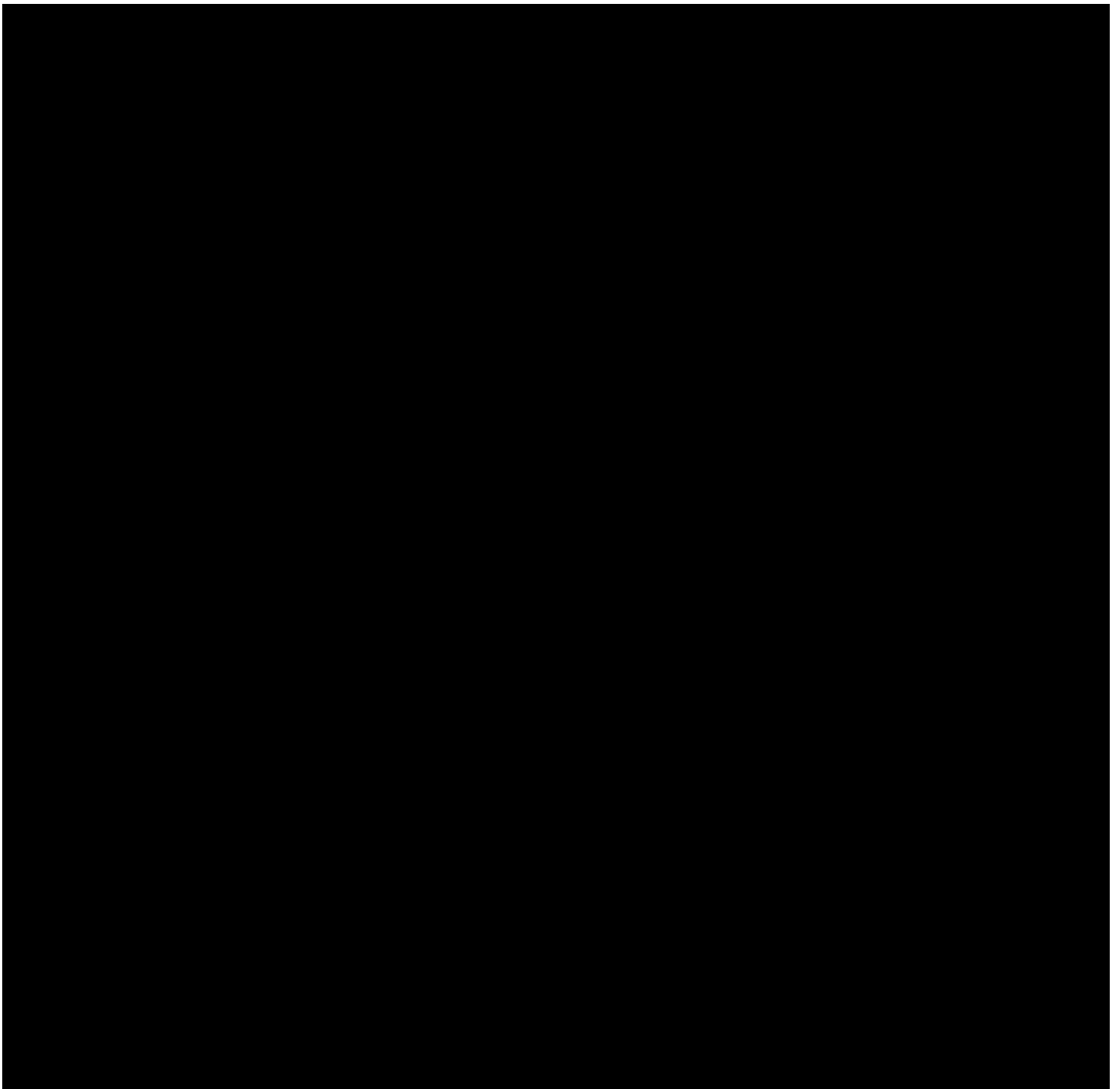












8.3 Overview of Efficacy Analysis Issues

8.3.1 Handling of Dropouts or Missing Data

The primary analysis will be completed with available data per subject from the 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]

8.3.2 Assessment Time Windows

In general, it is intended that all safety and efficacy data (with some exceptions) will be summarized at each scheduled time point collected regardless of assessment time windows. Because subjects may have an early termination visit at any time or may have unscheduled visits, the following conventions will be implemented.

For all by-visit statistical summaries, safety and efficacy data collected at early termination visits will be windowed into a scheduled study visit if the early termination visit falls within a protocol specified visit window. Visit 2 (Day 1) has to be on Day 1. Visit 3 (Day 14) and Visit 4 (Day 28) have a ± 2-day window. Visit 5 (Day 84) has -5/+2 day window. Unscheduled visits and early termination visits falling out of protocol specified scheduled visit windows will be excluded from summaries.

[redacted]

[redacted]

8.4 Analysis Methods

8.4.1 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

[redacted]

- Population: subjects with DED defined through enrollment criteria
- Endpoint:
    - Change from baseline in pre-CAE ODS-VAS at Day 28
    - Change from baseline in pre-CAE anesthetized Schirmer score at Day 28

[redacted]

The primary efficacy endpoints (e.g., change from baseline in pre-CAE ODS-VAS and change from baseline pre-CAE anesthetized Schirmer score) will be summarized using continuous summary statistics and analyzed separately using analysis of covariance (ANCOVA) models with terms for baseline value, treatment, and analysis center. In addition, the analysis center by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across analysis centers for the ITT population using available data.

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% CIs.

[redacted]

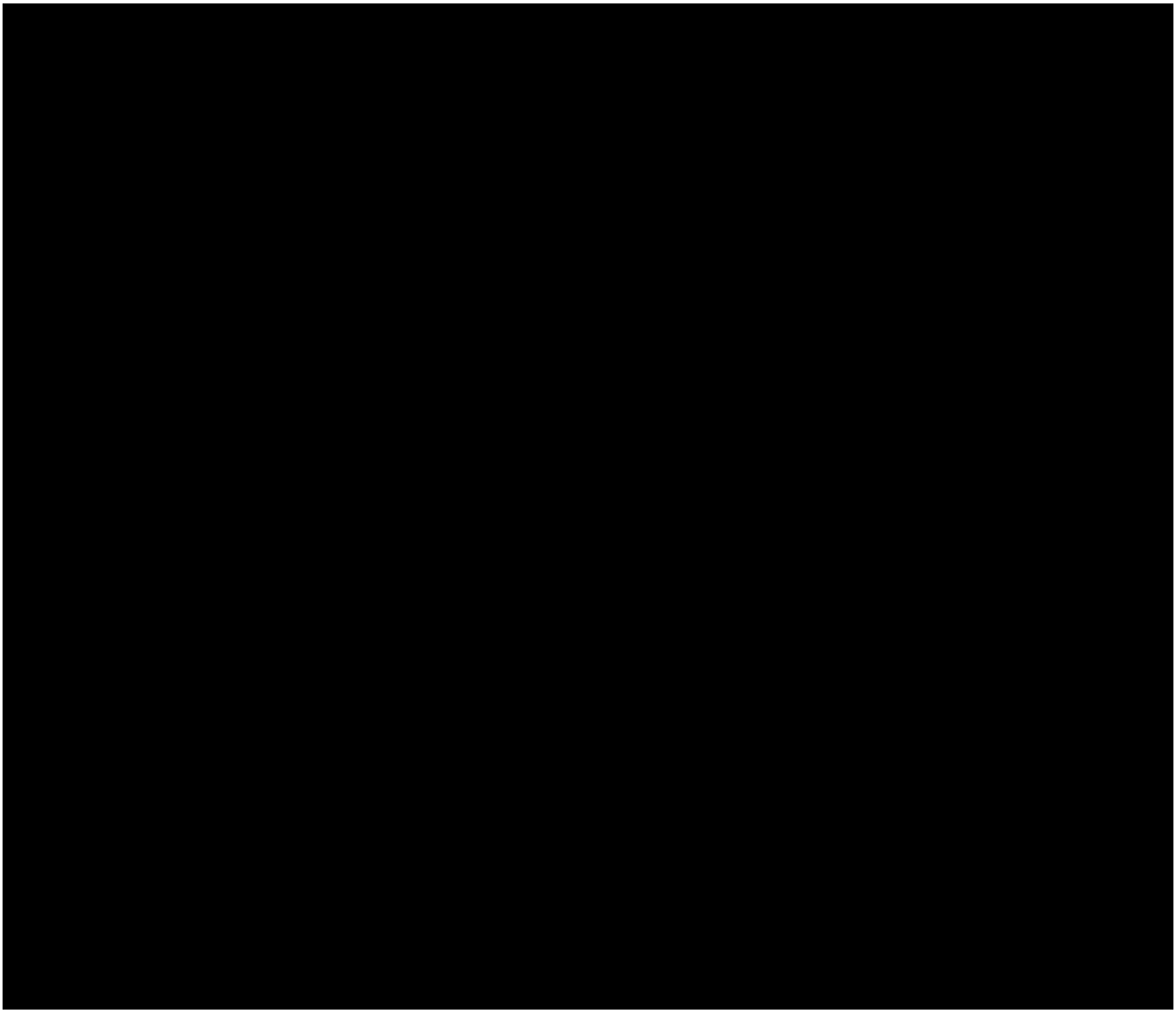
8.4.2 Secondary Efficacy Analyses

The secondary efficacy endpoints are listed in Section 8.2. The summaries and analyses of secondary efficacy endpoints will be conducted for the ITT population.

Summarization and analysis of secondary endpoints #1-30 (please refer to Section 8.2) will be completed using a similar strategy as for the primary endpoints.

Testing of the proportion of subjects with baseline anesthetized Schirmer scores ≤ 5 that achieved an anesthetized Schirmer score of ≥ 10 mm at Day 84 and Day 28 (#31 and #32, respectively) will be completed using logistic regression modes with fixed effects of treatment, corresponding baseline measure, and analysis center using available data, missing data imputed using LOCF, trimmed means, and MCMC multiple imputation methodology under assumption of missing (at random and not at random). The adjusted odds ratios and marginal proportions and difference in proportions along with corresponding two-sided 95% CIs and p-values will be presented. Treatment comparisons will also be made using Pearson's chi-squared test or Fisher's exact test if any of the cell counts are less than five as a sensitivity analysis to the primary model above and p-values will be provided.

[redacted]



9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

All safety analyses will be carried out using the Safety Population and will include the study eye and fellow eye separately, where applicable.

The assessment of safety will be evaluated by:

- Adverse events
- Slit-lamp biomicroscopy
- Dilated fundus exam
- Best Corrected Visual Acuity (BCVA)
- Intraocular pressure (IOP)

All safety variables will be descriptively summarized by treatment group at each assessment time and for relevant changes from baseline, where applicable.

For complete inclusion of subjects who withdraw from the study early, the End of Study visit for safety outcomes will be defined as either Visit 5 (Day 84) or Early Discontinuation.

9.2 Extent of Study Treatment Exposure

Summary statistics will be presented for treatment exposure. Treatment exposure will be defined as the number of days that the subject was exposed to study treatment as calculated using the formula:

$$\text{Treatment exposure} = \text{Date of Last Dose} - \text{Date of First Dose} + 1.$$

9.3 Adverse Events

Adverse events will be coded to SOC and PT using MedDRA, Version 23.0.

Treatment-emergent adverse events (TEAEs), those that occur on/after the first dose of assigned study treatment (i.e. during the randomized treatment period) at subject level, will be summarized by treatment group using frequencies and proportions for each SOC and each PT within a SOC.

Adverse events occurring during the vehicle run-in period will also be summarized.

The number and percentages of subjects with TEAEs (with onset during the randomized treatment period) listed below will be summarized by SOC, PT, and treatment separately. An overall summary table will be also developed to report the number of events and the incidence of subjects having at least one event in the categories below.

- TEAEs
- Serious TEAEs

- Treatment-Related SAEs (reported as possibly related or related to the investigational product)
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to investigational product discontinuation
- TEAEs resulting in death

While the overall summary of TEAEs with onset during randomized treatment period will present both the number of TEAEs and the incidence of TEAEs, the other summaries will only report the incidence of TEAEs. When reporting the number of TEAEs, if the same TEAE occurs for a subject on multiple occasions the event will be counted once for each occurrence. When reporting the incidence, a subject will only be counted once if they ever experience an event within the SOC and ever experience the individual PT. Summaries will be performed using the actual treatment received. Separate summaries will be performed for ocular and non-ocular AEs.

AEs that occurred during the vehicle run-in period will also be summarized by SOC and PT for the vehicle run-in population.

All AEs, serious AEs, and AEs leading to investigational product discontinuation will be listed in subject data listings separately.

9.4 Intraocular Pressure

Intraocular pressure will be presented in data listings. Intraocular pressure data will be summarized at each visit using continuous summaries, including change from baseline, for both the study eye and the fellow eye.

9.5 Best Correct Visual Acuity

The BCVA logarithm of the minimum angle of resolution (logMAR) score will be presented in data listings. BCVA data will be summarized at each visit using continuous summaries, including change from baseline, for both the study eye and the fellow eye. Additionally, discrete summaries of the worst change from baseline will be presented for both the study eye and the fellow eye with the following groupings based on the logMAR scores: 0 or less, >0 to +0.09, +0.10 to +0.19, +0.20 to 0.29, +0.30 or more.

9.6 Dilated Fundus Examination

Dilated fundus exam results at each visit will be presented in data listings. A separate listing will be created for those subjects with a criterion change, defined as a change from "Normal" to "Abnormal" or a change from "Abnormal – Not Clinically Significant" to "Abnormal – Clinically Significant."

Frequencies and percentages of normal and abnormal results will be created for the following fields: Vitreous, Retina, Macula, Choroid, and Optic Nerve. Abnormal results will further be

broken down by clinical significance and non-clinical significance. A shift from baseline in the results for study eyes and fellow eyes will also be summarized by treatment group.

9.7 Slit-Lamp Biomicroscopy

Biomicroscopy results will be listed at each visit. A separate listing will be created for those subjects with a criterion change, defined as a change from "Normal" to "Abnormal" or a change from "Abnormal – Not Clinically Significant" to "Abnormal – Clinically Significant."

Frequencies and percentages of normal, abnormal results will be created for the following fields: Cornea, Conjunctiva, Anterior Chamber, Iris, Lens, and Lid. Abnormal results will further be broken down by clinical significance and non-clinical significance. A shift from baseline in the results for study eyes and fellow eyes will also be summarized by treatment group.

[redacted]

11. INTERIM ANALYSES AND DATA MONITORING

This section is not applicable for this study.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

No changes to the analyses that are planned in the protocol.

13. REFERENCES

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320. (E3)

14. APPENDICES

Appendix 1 Schedule of Visits and Procedures

Study Day	**Start of 2 Week Run-In (AR-15512 Vehicle)**		**Treatment 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[a i(1)(a)(i)1 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)[a i(1)(a)(i)1 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)**		**Treatment 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)**		**Treatment 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
In office administration of study treatment		X		X	X		X			
[redacted]										
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]