A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease (COMET-2)

STUDY ID:

AR-15512-CS301

STATISTICAL ANALYSIS PLAN

NCT05285644

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Sponsor: Aerie Pharmaceuticals, Inc
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Durham, NC 27703

Protocol Number: AR-15512-CS301

[redacted]

Date: 07JUL2023
Version: 1.0

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[redacted]

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[redacted]

[redacted]

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List of Abbreviations

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BID	*Bis in die* (Twice Daily)
CAE®	Controlled Adverse Environment
CI	Confidence Interval
CS	Clinically Significant
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDS	Eye Dryness Score
ET	Early Termination
ETDRS	Early Treatment of Diabetic Retinopathy Study
FCS	Fully Conditional Specification
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IRT	Interactive Response Technology
ITT	Intent-to-Treat
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Non Clinically Significant
[redacted]	[redacted]
OD	*Oculus dexter* (Right Eye)
ODS	Ocular Discomfort Score
OU	*Oculus uterque* (Both Eyes)
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
[redacted]	[redacted]
RTF	Rich Text Format
SANDE	Symptom Assessment Questionnaire iN Dry Eye
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
[redacted]	[redacted]
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analog Scale

Abbreviation	Definition
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol AR-15512-CS301, Version 2.0 dated 13MAY2022, in addition to its associated Administrative Clarification Letter #1 dated 21JUL2022 and Clarification Letter #4 dated 16FEB2023.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline[1] entitled Guidance for Industry: Statistical Principles for Clinical Trials, the most recent ICH E9 (R1) Guideline[2] entitled Guidance for Industry: Statistical Principles for Clinical Trials: Addendum on the Estimands and Sensitivity Analysis in Clinical Trials, and the most recent ICH E3 Guideline[3], entitled Guidance for Industry: 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, which will supersede the clinical protocol. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

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

2.1 Study Endpoints

[redacted] efficacy endpoints in Section 2.1.1, Section 2.1.2, and Section 2.1.3 will be reported for study eye only unless otherwise specified in Section 13.4, Section 13.5, and Section 13.6 respectively. The “Baseline” in Section 2.1.1, Section 2.1.2, and Section 2.1.3 refers to Baseline (Day 1) visit unless otherwise specified.

2.1.1 Primary Endpoint

- Proportion of subjects with ≥ 10 mm increase (post-drop on Day 14 vs pre-drop at Baseline) in unanesthetized Schirmer score on Day 14

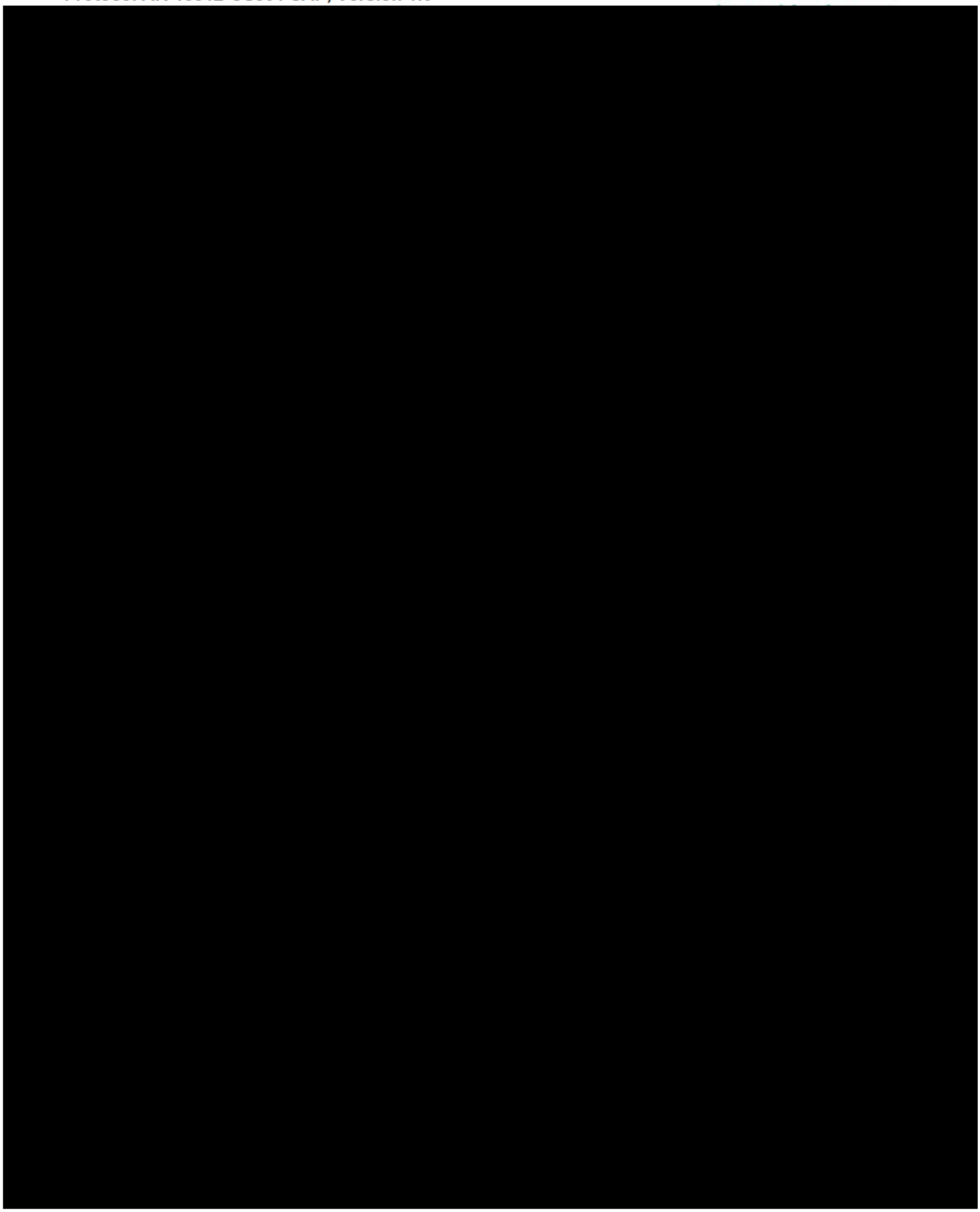
2.1.2 Secondary Endpoints

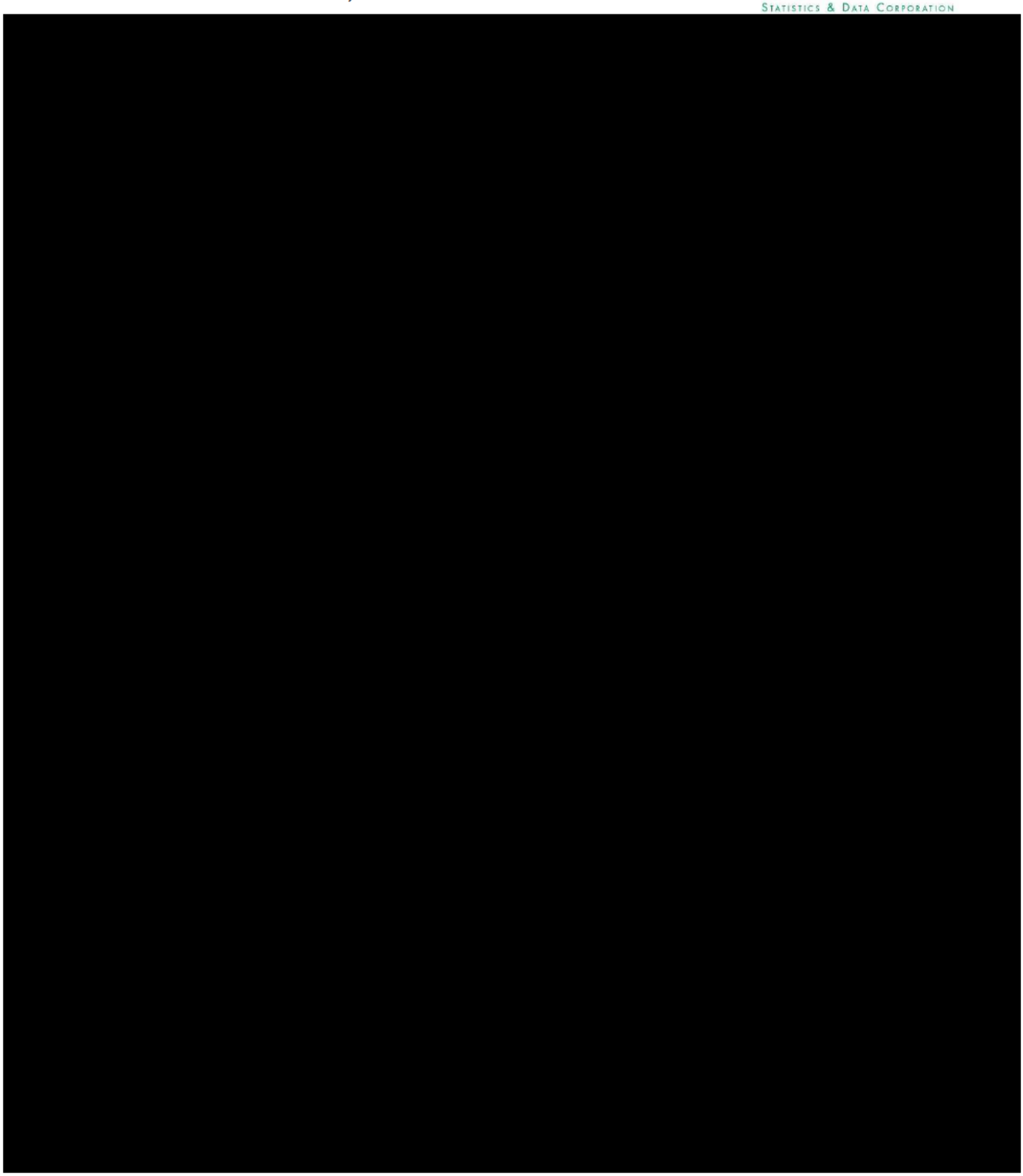
- Change from baseline in global symptom assessment in dry eye (SANDE) score on Day 28
- Change from baseline (post-drop on Day 14 vs pre-drop at Baseline) in unanesthetized Schirmer score on Day 14
- Proportion of subjects with ≥ 10 mm increase (post-drop on Day 1 vs pre-drop at Baseline) in unanesthetized Schirmer score on Day 1

- Change from Baseline (post-drop on Day 1 vs pre-drop at Baseline) in unanesthetized Schirmer score on Day 1
- Proportion of subjects with ≥ 10 mm increase (post-drop on Day 90 vs pre-drop at Baseline) in unanesthetized Schirmer score on Day 90
- Change from baseline (post-drop on Day 90 vs pre-drop at Baseline) in unanesthetized Schirmer score on Day 90
- Change from baseline in global SANDE score on Day 90
- Change from baseline in SANDE frequency score on Day 90
- Change from baseline in SANDE severity score on Day 90
- Change from baseline in eye dryness score (EDS) – VAS on Day 90
- Change from baseline in ocular discomfort score (ODS) – visual analog scale (VAS) on Day 90

[redacted]

[redacted]





2.1.4 SAFETY VARIABLES

The safety variables include the following:

- Adverse events (AEs)

- Hematology, chemistry, and urinalysis
- Vital signs (heart rate and blood pressure)
- Corrected visual acuity
- Slit-lamp biomicroscopy
- Intraocular pressure (IOP)
- Dilated fundus exam

2.2 Statistical Hypotheses

The primary endpoint will be tested as follows:

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

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

2.3 Estimands

2.3.1 Estimand 1 (Primary Estimand)

The primary comparison will be based on the ITT population targeting the treatment effect attributable to the randomly assigned treatment, regardless of compliance to study treatment and assuming subjects who discontinued due to lack of efficacy, AEs, or disallowed concurrent treatments follow the behavior of subjects in the reference arm for the duration of the study and subjects who discontinued for other reasons (outside of lack of efficacy, AEs or use of disallowed treatment) would follow the behavior of subjects who are still in the study under same randomly assigned treatment.

- Population: subjects in the ITT population with DED defined through enrollment criteria
- Endpoint:
  - Proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14
- Intercurrent event:
  - Non-optimal treatment compliance is ignored. [treatment policy strategy]
  - Withdrawal due to lack of efficacy, AEs, or disallowed concurrent treatment - multiple imputations using vehicle treatment group regardless of randomized treatment group is used to impute missing data. [hypothetical strategy, missing not at random]
  - Withdrawal due to reasons other than lack of efficacy, AEs, or disallowed concurrent treatment - multiple imputations using randomized treatment is used to impute missing data. [hypothetical strategy, missing at random]

- Population-level summary:
    - Difference in the proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14 between AR-15512 (0.003%) and vehicle

[redacted]

[redacted]

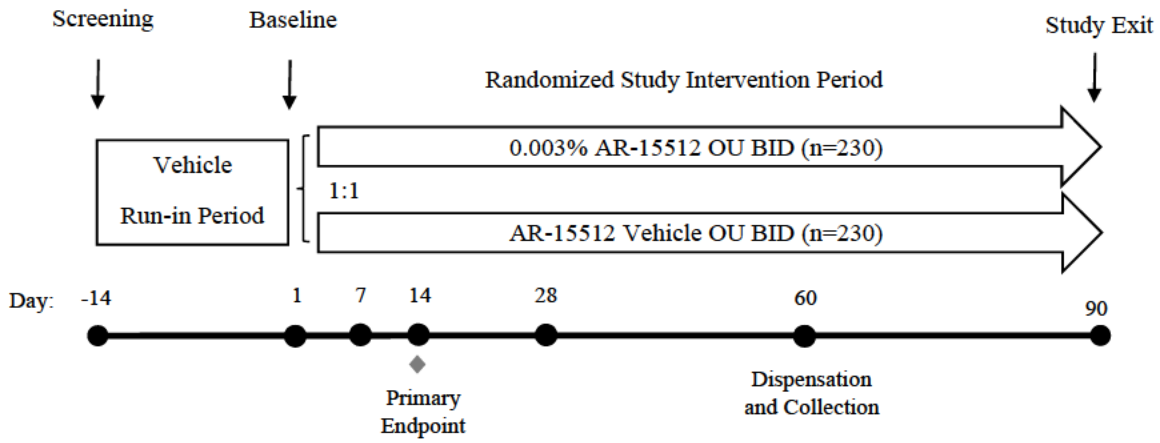
3. Study Design and Procedures

3.1 General Study Design

This will be a Phase 3, multicenter, vehicle-controlled, double-masked, randomized study conducted at approximately 20 sites in the United States. All subjects enrolled will have DED. The study will consist of Screening (Day -14) and Baseline (Day 1) visits as well as follow-up visits on Day 7, Day 14, Day 28, and Day 90 (Study Exit). There will also be a Day 60 dispensing visit. All subjects will be exposed to the Controlled Adverse Environment (CAE®) at the Screening visit.

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

Figure 1. Study Design



Scheduled study visits in Table 1 (Screening, Baseline [Day 1], Day 7, 14, 28, 60, 90/Study Exit) will be referred as such in all tables and listings to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. There is no Day 0, and Day 1 is the day of randomization, on which the subjects receive their first study intervention administration. For any event (or assessment) on or after Day 1, actual study day will be calculated as, (Date of Event) – (Date of First Dose of Study Intervention) +

1. For an event before Day 1, actual study day will be calculated as, (Date of Event) – (Date of First Dose of Study Intervention).

3.2 Schedule of Visits and Procedures

The Schedule of Visits and Procedures is shown in Table 1.

.

Table 1 Schedule of Visits and Procedures

According to the Clarification Letter #1, anesthetized Schirmer test is scheduled at both Screening and Baseline (Day 1) visit as stated in protocol Section 7.2. The schedule of visits in the table doesn't have Baseline (Day 1) visit marked.

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

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

[1] All office visits must be arranged at approximately the same time of day ± 1 hour.
[2] The Baseline visit should be scheduled between 11 and 14 days after the Screening visit. If absolutely necessary, the Baseline visit may be delayed up to 7 days (extending the run-in period to a maximum of 21 days).
[3] Administered every 5 minutes while in the CAE.
[4] Day 7 Randomized Intervention Kit is not to be dispensed home to the subject. A single vial is used at the Day 7 visit and then returned to the kit. The single used vial as well as remaining 4 unused vials are to be retained for accountability.
[5] Study intervention must be removed from the refrigerator at least 30 minutes before use.
[6] Dispensing and collection visit only.

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

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

All qualified subjects will be assigned to receive AR-15512 vehicle BID to both eyes for approximately 14 days during the vehicle run-in period. Following the run-in period, all subjects who requalify at Baseline (Day 1) will be randomized in a 1:1 ratio, within each site, to receive 0.003% AR-15512 or AR-15512 vehicle. The IRT will provide the site with the specific kit number(s) for each randomized subject at the time of randomization. Sites will dispense the study intervention according to the IRT instructions and the Schedule of Visits and Assessments as in Table 1.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened for eligibility up to one time if there is reasonable possibility, in the Investigator's opinion, that the patient might meet the eligibility criteria. When a subject is rescreened, a new subject ID will be assigned, and the previous subject id will be recorded in the Informed Consent CRF form.

The subject ID will be in the format of xxx-xxx, with the first 3 characters being the site number and the last 3 characters sequentially numbered starting from 001 within the site, which will be used to identify subjects in all datasets and listings for this study.

4.2 Masking and Unmasking

4.2.1 MASKING

During the vehicle run-in period, the subject will be masked. During the randomized study intervention period, the Investigator and site staff performing eligibility/efficacy and safety assessments and the subjects will be masked. Subjects will remain masked during the randomized phase. Subjects will be informed that they all will receive vehicle at some point in the study, but the exact timing will not be specified. AR-15512 (0.003%) and AR-15512 vehicle will be provided in identical single-use blow-fill-seal containers.

4.2.2 UNMASKING

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

Study intervention assignments will be masked to the Investigator, the clinical study team (Sponsor, personnel involved in day-to-day study management, Monitors, Data Managers, and Statisticians), and the subjects. Only in case of medical emergency or occurrence of AEs that warrant unmasking in the opinion of the Investigator, will the study intervention assignment(s) be unmasked and made available to the

Investigator and the Medical Monitor. In the absence of medical need, the randomization code will not be available to the above personnel until after the study is completed and the database is locked.

If the Investigator feels it is necessary to unmask a subject's study intervention assignment after an emergency situation, the Investigator should contact the Medical Monitor or designee. Only after consultation with the Medical Monitor will a decision be made as to whether or not the study intervention for the subject should be unmasked. The study intervention assignment will be revealed on a subject-by-subject basis, thus leaving the masking on the remaining subjects intact.

5. Sample Size and Power Considerations

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

Additionally, 202 ITT population subjects (study eyes) per treatment group yields 99% power to conclude superiority of 0.003% AR-15512 over vehicle in the mean change from baseline in SANDE score on Day 28 assuming a true difference (AR-15512 minus vehicle) of -8.3, a common standard deviation (SD) of 17.72, and a two-sided alpha=0.05.

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

6. Data Preparation

6.1 Input Data

Study data will primarily be recorded on the electronic Case Report Forms (eCRFs) supplied by Statistics & Data Corporation (SDC) using electronic data capture (EDC) system, Medidata RAVE. In addition, the following study data which is not captured directly within the EDC system but is obtained from external vendors will also be included for analysis. These data sources are described in detail in data transfer agreements developed between data management and the respective external laboratory:

- Central laboratory data from ACM Global Laboratories (hematology, chemistry, and urinalysis)

When all prerequisites for database lock have been met, including availability of all masked external data, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

Final analysis will be carried out after the following have occurred:

- Database lock has occurred, including receipt of all final versions of external vendor data, with written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

6.2 Output Data

Data from EDC and external data will be transferred to SDC Biostatistics and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM version 1.7 model and will be implemented using the SDTM Implementation Guide version 3.3 and the most recent SDTM Controlled Terminology version at the time of programming start. ADaM data will follow the ADaM version 2.1 model and will be implemented using the ADaM Implementation Guide version 1.1. Both SDTM and ADaM will be validated using Pinnacle 21 version 4.0.0 or above. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers. The actual versions will be determined at the time of programming start.Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model or above.

7. Analysis Populations

7.1 Intent-to-Treat

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

7.2 Per Protocol

The Per Protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations likely to seriously affect the primary outcome of the study and who complete the trial through Day 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.

7.3 Safety

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.

[redacted]

8. General Statistical Considerations

8.1 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints assessed at the eye level, the unit of analysis will be the "study eye" as defined in Section 8.2. For efficacy endpoints assessed in both eyes (OU), the unit of analysis with be the subject.

8.2 Study Eye Selection

The study subject must have at least one eye (the same eye) meeting all the inclusion criteria and none of the exclusion criteria at both Screening and Baseline (Day 1) visits where applicable. Study subjects will be dosed in both eyes. If both eyes are eligible at the time of randomization, the study eye will be defined as the eye with the lower pre-drop unanesthetized Schirmer score at the Baseline (Day 1) visit. If both eyes still qualify and have the same pre-drop unanesthetized Schirmer score, the right eye (OD) will be designated as the study eye.

Study eye will not be directly collected in EDC. Instead "Qualifying Eye" will be collected at Baseline (Day 1) visit. When one eye is the qualifying eye, then it will be the study eye. If both eyes are qualified, then study eye will be derived programmatically based on study eye selection criteria in this section. The non-study eye will be referred to as the fellow eye.

8.3 Missing or Inconclusive Data Handling

8.3.1 Missing Efficacy Assessments

The primary analysis will be based on MI methodology as specified in Estimand 1 (Section 2.3.1) [redacted]

[redacted]

8.4 Definition of Baseline

Baseline is defined as the last non-missing measure prior to the initiation of randomized study intervention.

- The efficacy endpoint baseline will be the Baseline (Day 1) measurement. Screening visit and unscheduled visit measurements if any prior to the initiation of randomized study intervention **will not be considered** for baseline even when Baseline (Day 1) measurement is missing.
- For unanesthetized Schirmer test measures taken at both pre-drop and post-drop, the pre-drop measure at Baseline (Day 1) will be the baseline for primary and secondary analyses as specified

in Sections 2.1.1 and 2.1.2, [redacted]

- The safety endpoint baseline will be the Baseline (Day 1) measurement. When Baseline (Day 1) measurement is missing, the last non-missing measurement from Screening visit and unscheduled visit measurements prior to the initiation of randomized study intervention **will be considered** for baseline.

8.5 Data Analysis Conventions

All data analysis will be performed by SDC. 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 using landscape orientation.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, SD, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Change from baseline will be calculated as, Post-Baseline Result – Baseline, and treatment comparisons will be calculated as, AR-15512 (0.003%) – Vehicle.

All statistical tests will be two-sided with a significance level of 0.05 (α=0.05) unless otherwise specified. Confidence intervals (CIs) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as “<0.0001”; p-values greater than 0.9999 will be presented as “>0.9999.”

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit. Listings will be presented by treatment group, subject number, visit/time point, and parameter as applicable using all randomized subjects. Early termination visit (ET) and unscheduled visits will not be summarized in table summaries and will only be presented in listings.

[redacted]

8.7 Multicenter Consideration

Analyses adjusting for analysis center will be conducted. Analysis centers are the same as investigative sites if the number of randomized subjects in a site is equal to or larger than 10. All investigative sites with number of randomized subjects in a site less than 10 will be pooled into an analysis center for analyses.

9. Disposition of Subjects

Disposition will be presented in terms of numbers and percentage of subjects by treatment group and for all subjects. Percentages will be calculated using number of randomized subjects as the denominator unless otherwise specified.

The number of subjects screened, screen failed, entered run-in period, and randomized will be presented. Provided that subjects may be rescreened once after initial screen failure, each subject will be reported based on his/her final enrollment status, i.e., screen failure, randomized.

The number and percentages of subjects in each analysis population (ITT, PP, and Safety) will be presented.

The number and percentages of subjects who completed the study or discontinued from the study will be presented. The reasons for study discontinuation to be summarized will include AE, withdrawal of consent, non-compliance, lost to follow-up, disallowed concurrent treatment, pregnancy, lack of efficacy, investigator decision, protocol deviation, death, and other.

The number and percentages of subjects with any protocol deviation, major deviation, minor deviation, or COVID-19 related deviation will be presented.

Subject listings including subject disposition for randomized subjects and screen failed subjects separately, informed consent, violation of inclusion/exclusion criteria, protocol deviations, and analysis populations, will be provided. In addition, details of the study randomization, including randomization date and time, randomized treatment, actual treatment, qualifying eye, and study eye will also be included in a subject listing.

10. Demographic, Baseline Characteristics, and Other Pre-treatment Variables

10.1 Demographic and Baseline Characteristics

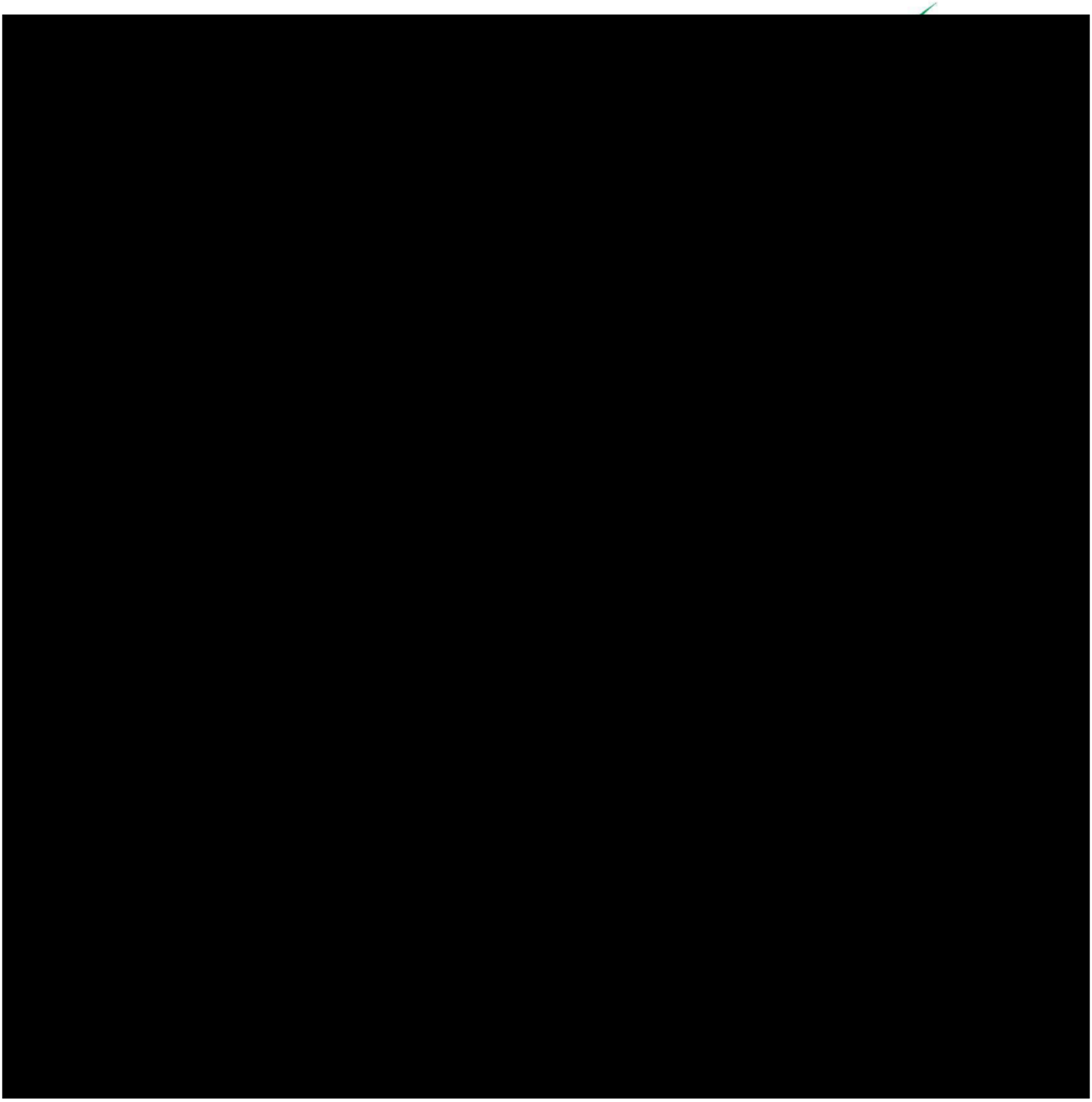
The demographic variables collected in this study include age, sex assigned at birth, childbearing potential for female subjects and method of contraception for female subjects with childbearing potential, race, ethnicity, and iris color. Subjects who record more than one race will be grouped into a single category denoted as Multi-racial. Iris color will be summarized at the subject level for study eye and fellow eye separately. Demographic variables will be summarized using ITT population and Safety population separately.

Age (years) will be summarized, overall and by treatment group, using continuous descriptive statistics. Age will also be categorized as follows: 30 – 45 years, 46 – 60 years, 61 – 75 years, and > 75 years. The number and percentage of subjects will be presented, overall and by treatment group, for age category, sex, race, ethnicity, and iris color of both study eye and fellow eye.

[redacted]

A subject listing that includes all demographic variables will be provided. In addition, subject listings will be provided for the childbearing potential and pregnancy test results, separately, for female randomized subjects.

[redacted]



11. Medical History, Prior and Concomitant Medications, and Concomitant Procedures

11.1 Medical History

Medical history will be obtained at the Screening visit and coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 and summarized using Safety population.

Ocular medical history and non-ocular medical history will be summarized separately using discrete summary statistics, overall and by treatment group, at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the Safety population. Percentages will be based on the number of subjects in

each treatment group. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. If a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs and PTs within a SOC are listed in order of descending frequency across all subjects.

Subject listings of medical history will be generated separately for ocular and non-ocular data.

11.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (B3, March 2022) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then the next highest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name.

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study intervention administration and continuing for any period of time following the first administration of study intervention or (2) at any time on or after the first administration of study intervention.

Ocular and non-ocular concomitant medications will be summarized separately using the Safety population. Medications will be tabulated by treatment group using frequencies and percentages. Subjects may have more than one medication per ATC. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. In the summaries, ATC classes and preferred names within an ATC class will be listed in order of descending frequency across all subjects.

A subject listing of prior and concomitant medications will be generated.

11.3 Concomitant Procedures

Concomitant procedures or surgeries performed during the study period will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 and presented in a subject listing.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

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

The subjects' used and unused study intervention vials will be collected on the Treatment Accountability Log eCRF page from the Baseline (Day 1) visit up to and including the Day 90 (or Early Termination [ET]) to assess dosing compliance. If the subject's compliance between visits is less than 80% or more than 125% based on the expected number of used and unused vials, then the subject will be deemed non-compliant, and a protocol deviation must be recorded. The study centers will keep an accurate accountability record that specifies the amount of study intervention dispensed to each subject, the amount of study intervention returned to the site, and the dates of each.

Overall study intervention dosing compliance (% compliance) starting from Baseline (Day 1) to Day 90 (or ET) will be assessed by:

$$\text{Compliance (\%)} = \frac{\text{Number of Actual Doses Received}}{\text{Number of Expected Doses}} \text{ x } 100$$

The number of actual doses received is calculated as the following:

(sum of "Number of Vials Used" recorded on Treatment Accountability Log) + 1

The adjustment of +1 will be applied to subjects who have Day 90 in-office dosing completed after the Treatment Accountability Log for Day 60 kits are recorded.

The number of expected doses is calculated as the following:

2 x (Date of Last Dose - Date of First Dose) + 1

for all subjects, regardless of study completion status. The adjustment of +1 is because there will be only one "evening" dose on the day of the first dose and two doses are expected for all other days till study exit. The date of last dose is the latest non-missing dosing date collected on the Study Drug Administration eCRF page or the Study Exit eCRF page, and the date of first dose is collected on the Study Drug Administration eCRF page.

Dosing compliance will be summarized numerically using continuous descriptive statistics and categorically (< 80%, >= 80% and <= 125%, and > 125% compliance) using counts and percentages for each treatment group using Safety population. When subjects have abnormal data entries caused by data issues, dosing compliance may not be calculated. Subject listings of study drug dispensation, treatment kit accountability, and in-office study drug instillation will be provided. In addition, a subject listing for run-in administration and dispensation will be provided separately.

12.2 Treatment Exposure

Treatment exposure will be defined as the number of days that the subject was exposed to study intervention as calculated using the formula:

Treatment Exposure Duration (days) = Date of Last Dose - Date of First Dose + 1.

Treatment exposure duration in days for each subject will be summarized with continuous descriptive statistics for each treatment group using the Safety population. The date of last dose is the latest non-missing dosing date collected on the Study Drug Administration eCRF page or Study Exit eCRF page, and the date of first dose is collected on the Study Drug Administration eCRF page.

13. Efficacy Analyses

Primary, secondary, [redacted] assessments are described in Section 13.1, Section 13.2, [redacted]. Subject listings will be produced for each efficacy assessment. In addition, the primary, secondary, [redacted] analyses are specified in Section 13.4, Section 13.5, [redacted]y.

13.1 Primary Efficacy Assessments

13.1.1 Unanesthetized Schirmer Test

Schirmer's test determines whether the eye produces enough tears to keep it moist. Two unanesthetized Schirmer tests (one pre-drop test and one post-drop test) for each eye will be performed at Baseline (Day 1), and Days 7, 14, 28, and 90. Greater Schirmer scores indicate greater amount of tears produced (or better results).

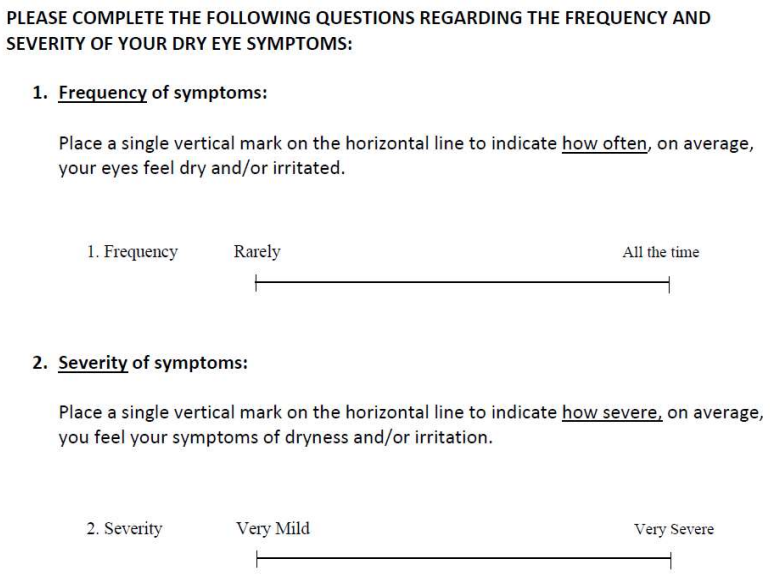
13.2 Secondary Efficacy Assessments

13.2.1 Symptom Assessment in Dry Eye Questionnaire

The SANDE questionnaire[4] is comprised of 2 unique VASs to assess the frequency and severity of DED symptoms. Subjects will be asked to complete the SANDE to rate both the frequency and severity of DED symptoms for both eyes together. Each of the two questions will be accompanied by a VAS. The assessment line length of the scale will be 100 mm and will be similar to the following depiction (Figure 3). Higher scores indicate greater frequency or severity of symptoms of dryness and/or irritation. In addition, a global SANDE score is also collected in the eCRF, which is calculated by multiplying the frequency score by the severity score and obtaining the square root rounded to the nearest whole number.

The SANDE will be administered at Screening, Baseline (Day 1), and Days 7, 14, 28, and 90. The frequency, severity and global SANDE score will be summarized.

Figure 3. SANDE Questionnaire Example



13.2.2 SYMPTOM QUESTIONNAIRE

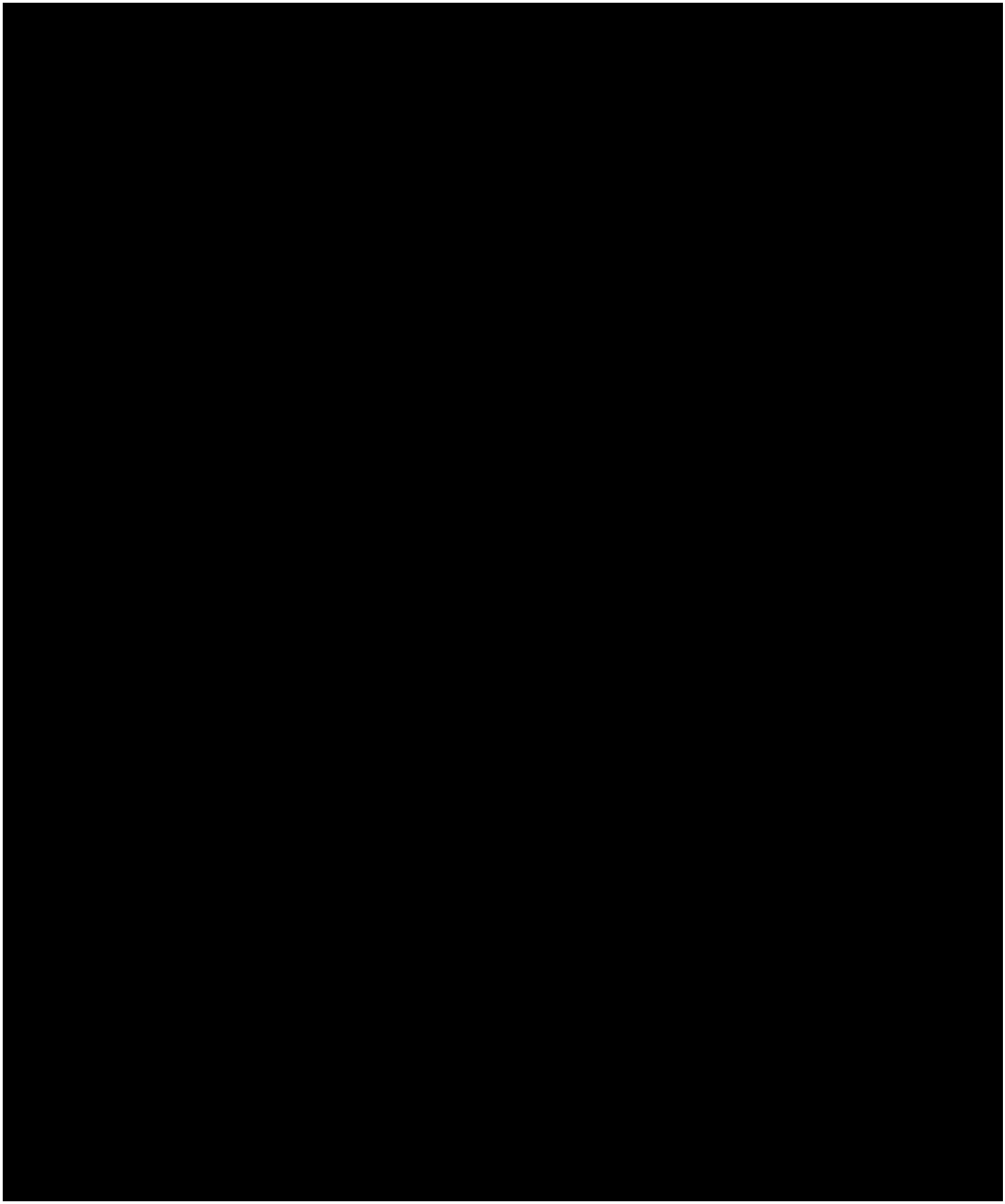
Subjects will be asked to rate each of the following DED symptoms (OU), over the last 24 hours, each on a separate VAS: ocular discomfort (ODS), eye dryness (EDS), [redacted] For each VAS, subjects will be asked to place a vertical mark on the horizontal line to indicate the level of each symptom, with 0 corresponding to "No Symptom" and 100 corresponding to "Maximal Symptom". The assessment line length of the scale will be 100 mm and will be similar to the following depiction (Figure 4). The questionnaire will be administered at Screening, Baseline (Day 1), and Days 7, 14, 28, and 90. The ODS, EDS, [redacted] scores will be summarized separately.

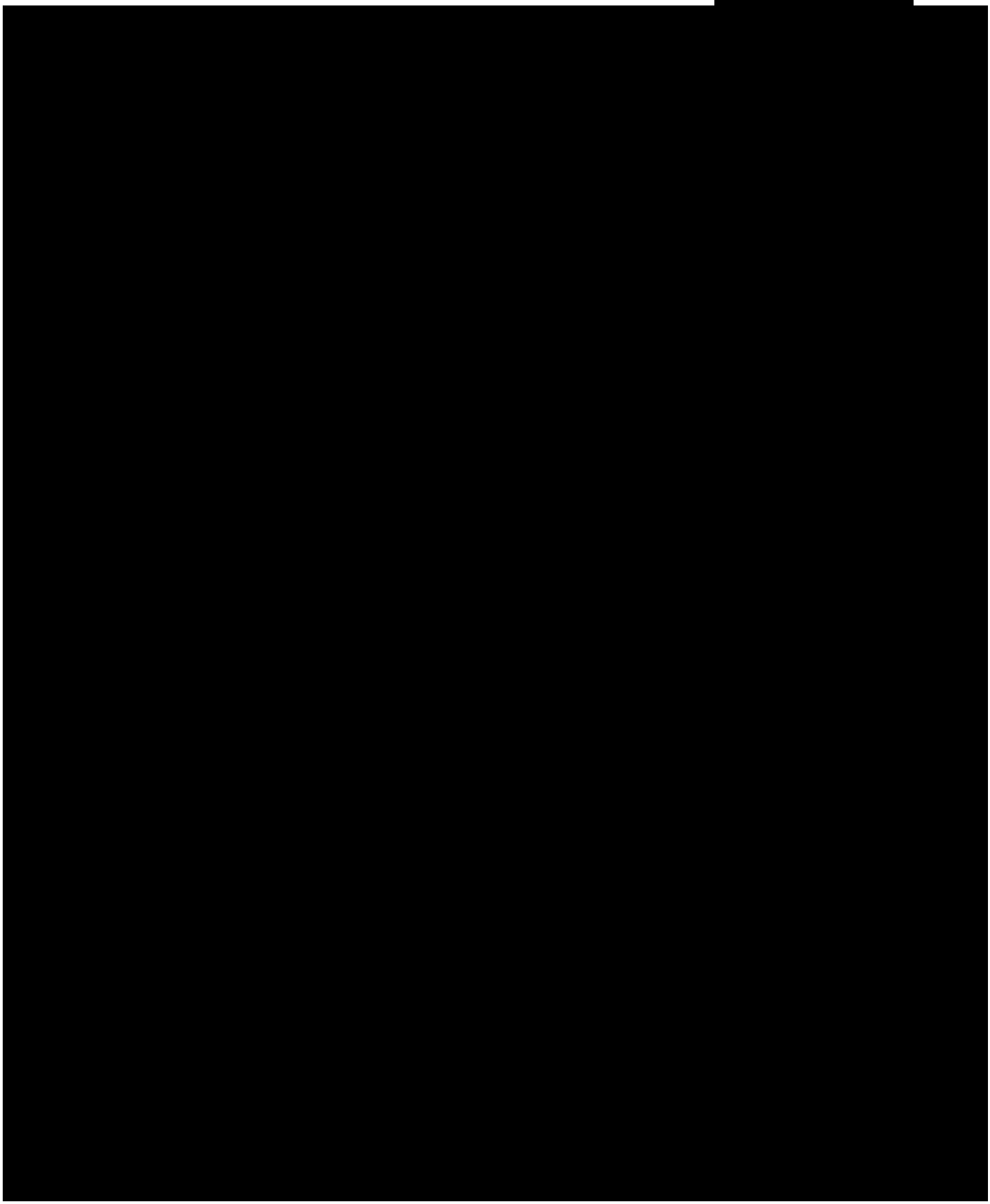
Figure 4. Symptom Questionnaire Example

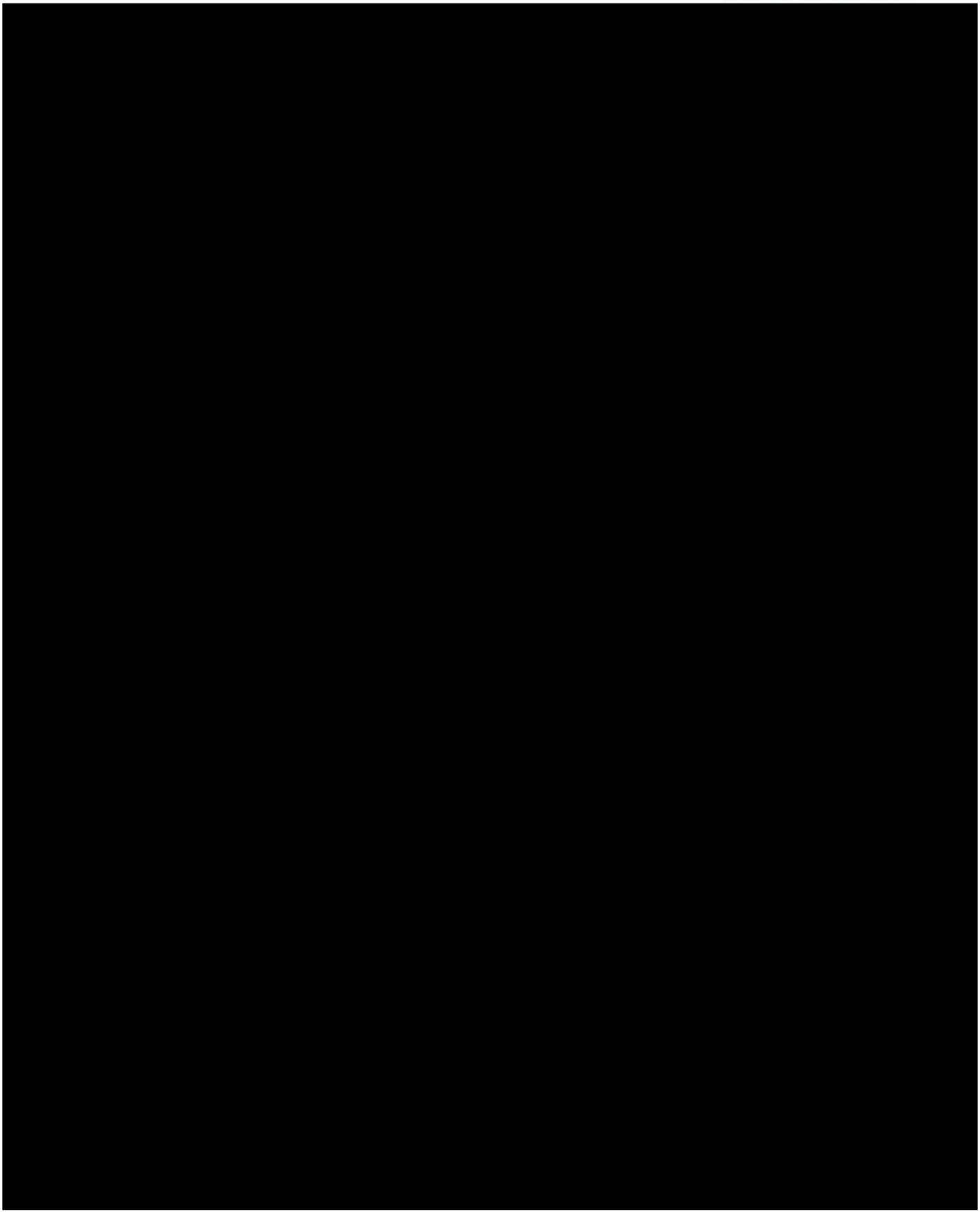
Ocular Discomfort: Visual Analog Scale

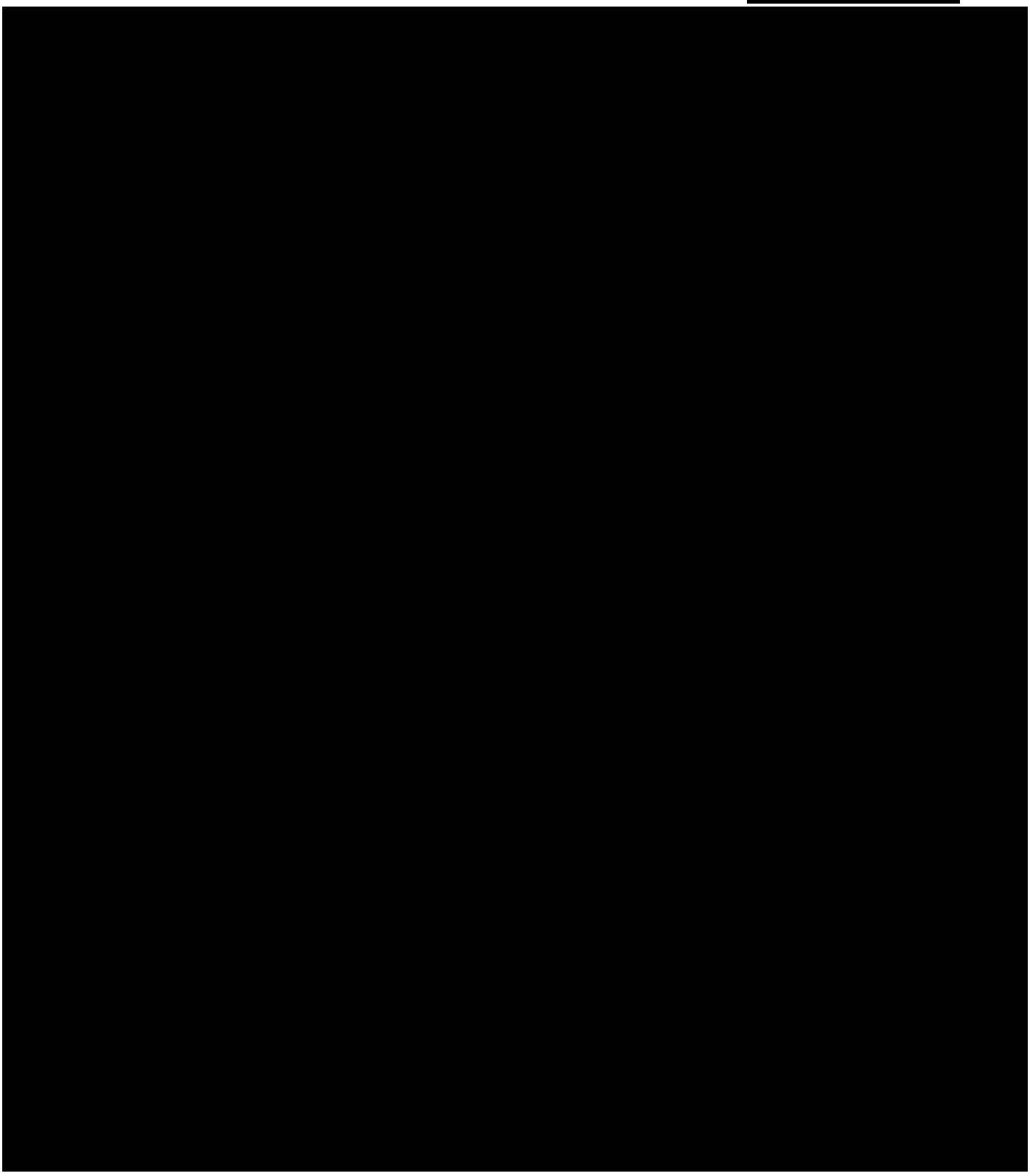
Eye Dryness: Visual Analog Scale

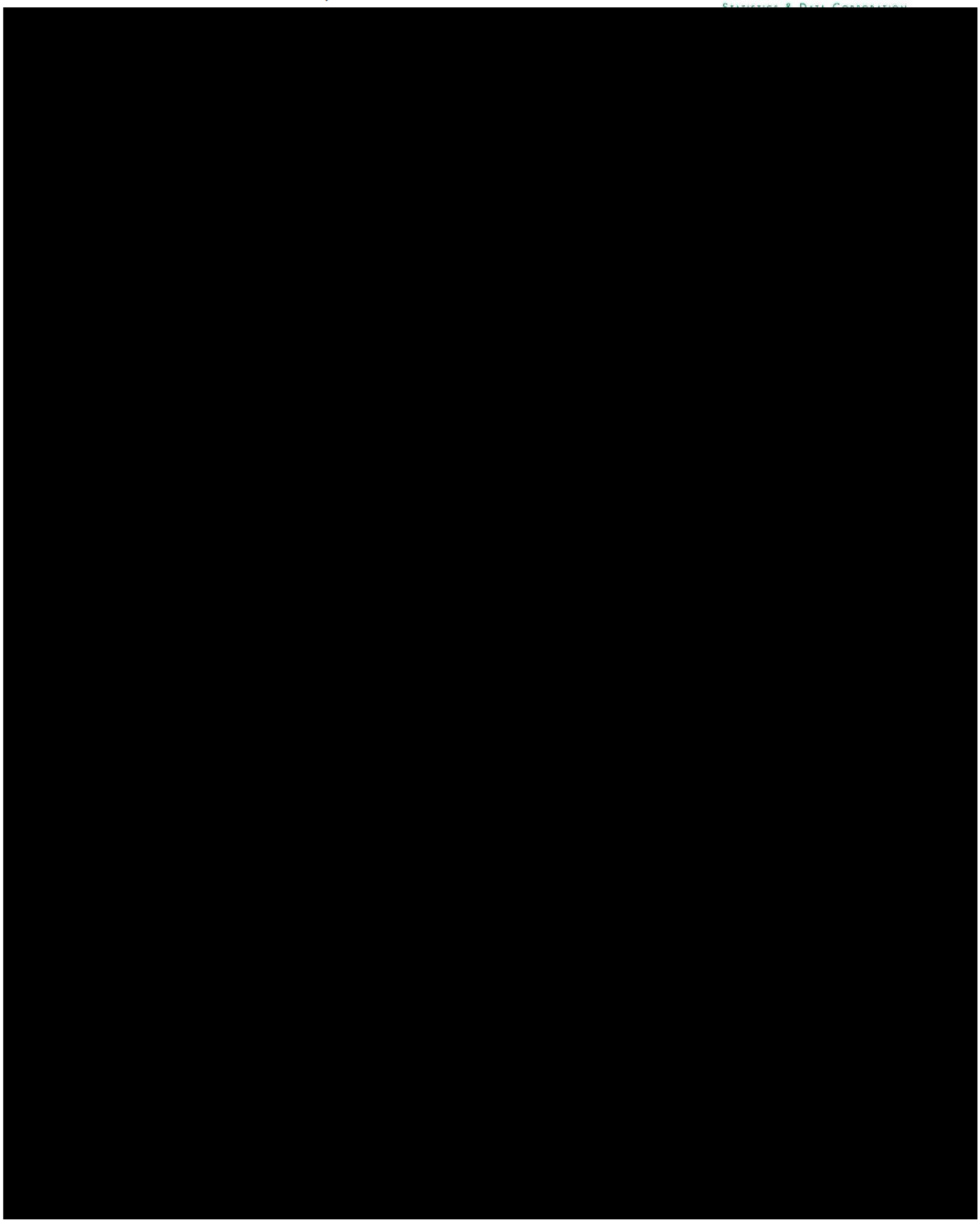
[redacted]











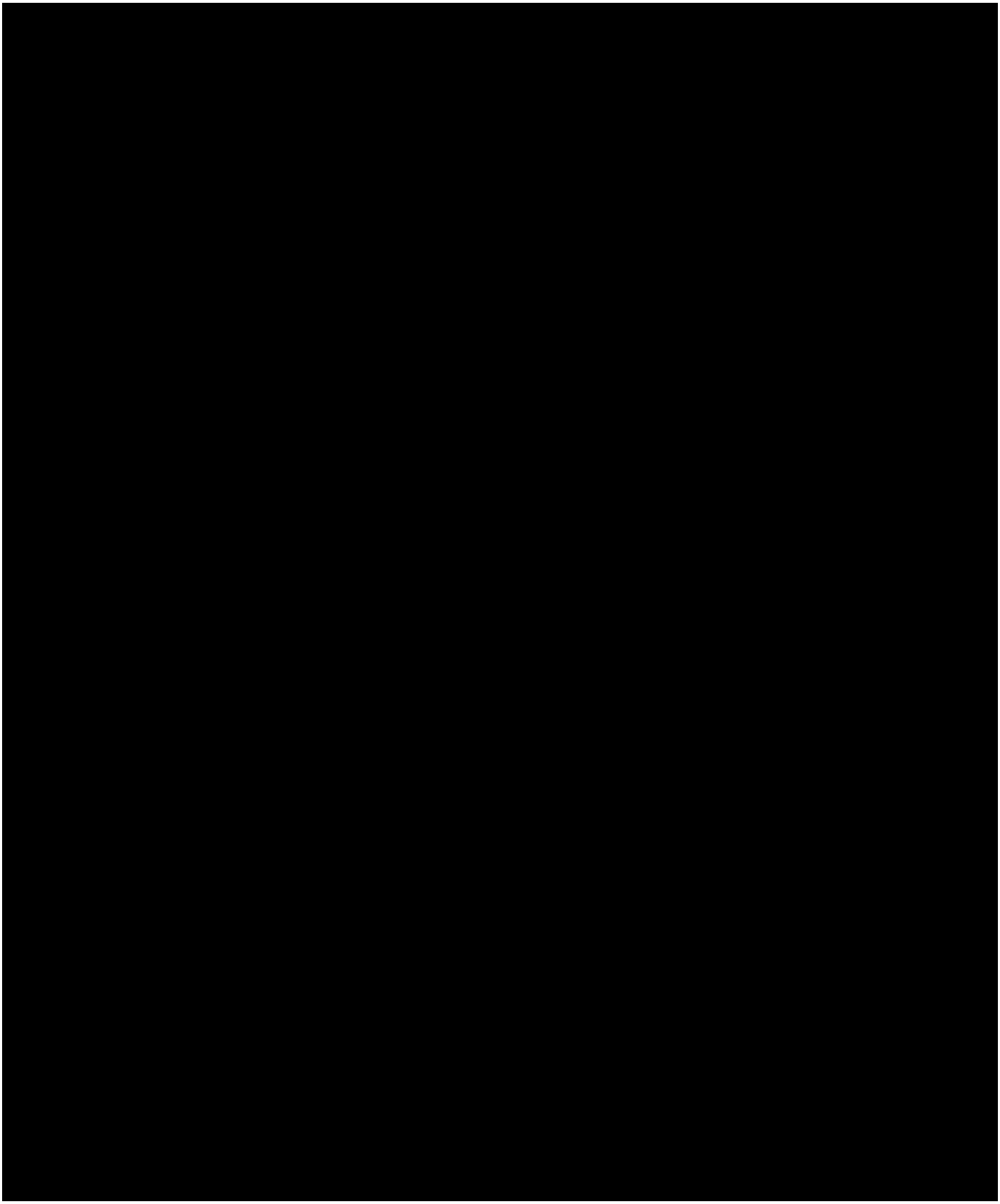
[redacted]

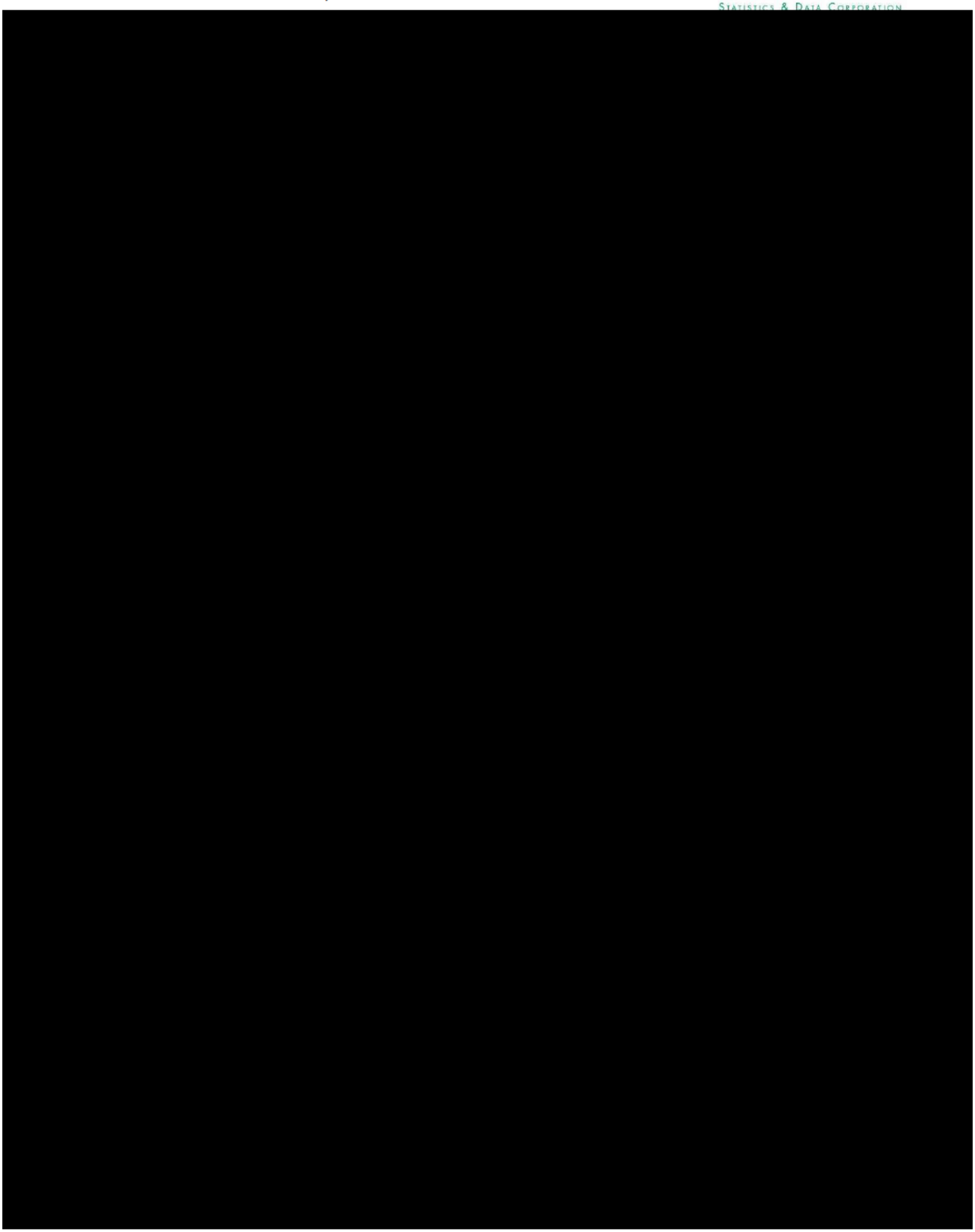
13.4 Primary Efficacy Analysis

The primary comparison in this trial will be between AR-15512 (0.003%) and vehicle in the ITT population using Estimand 1 (Section 2.3.1).

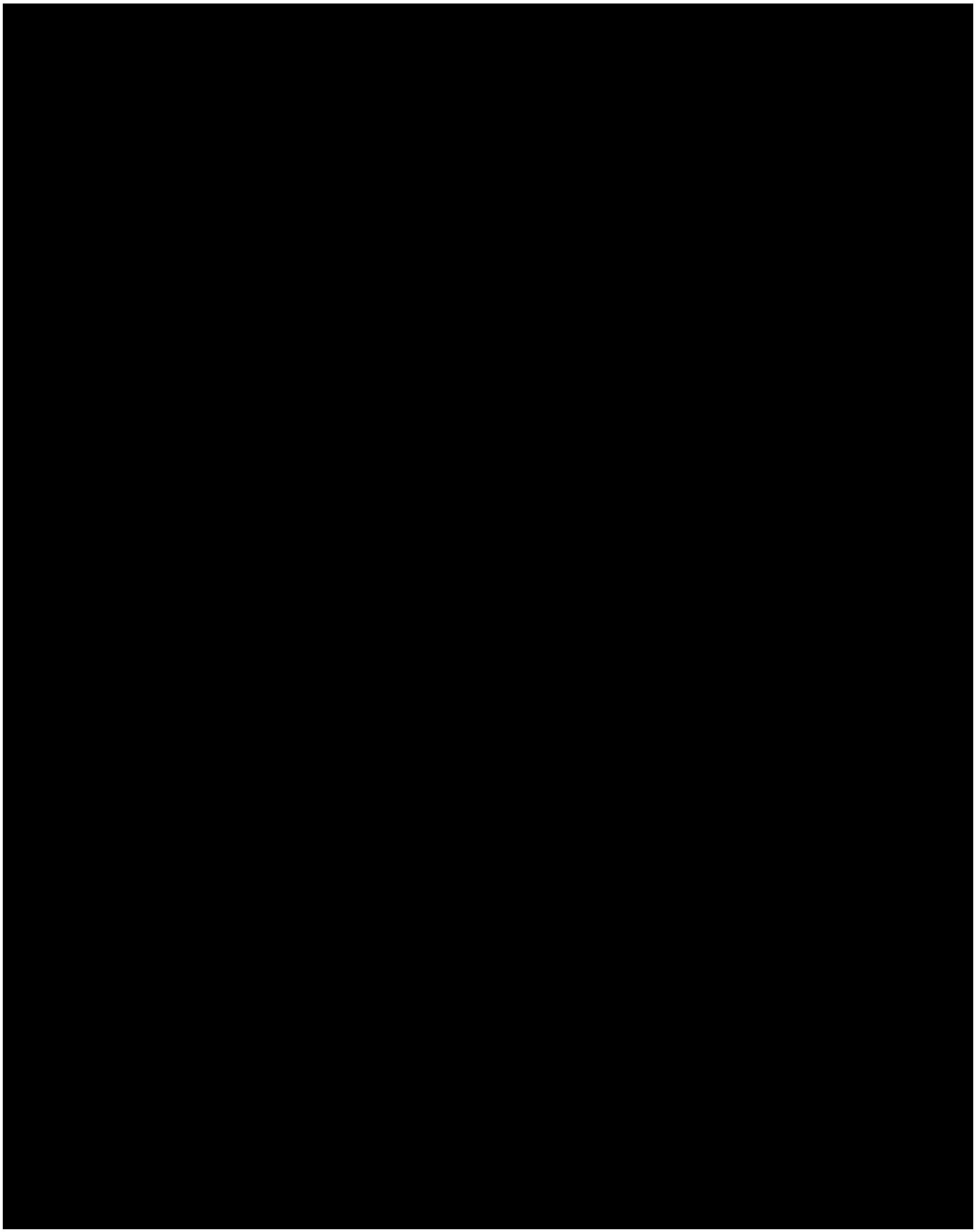
The frequency and percentage of subjects with ≥ 10 mm increase (Post-drop Measure on Day 14 – Pre-drop Measure at Baseline [Day 1]) in unanesthetized Schirmer score will be summarized by treatment group. Testing of the difference in proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14 will use Pearson's Chi-square test. The differences in proportions along with corresponding two-sided 95% CIs based on asymptotic normal distribution and p-values from Pearson's Chi-square test will be presented. [redacted]

[redacted]





[redacted]



[redacted]

13.5 Secondary Efficacy Analyses

The secondary efficacy endpoints are listed in Section 2.1.2. Changes from Baseline will be summarized by treatment group using continuous summary statistics and analyzed using an analysis of covariance (ANCOVA) model with terms for baseline value, treatment, and analysis center. [redacted] Least squares (LS) 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].

Specifically, the global SANDE as well as SANDE severity and SANDE frequency scores will be analyzed:

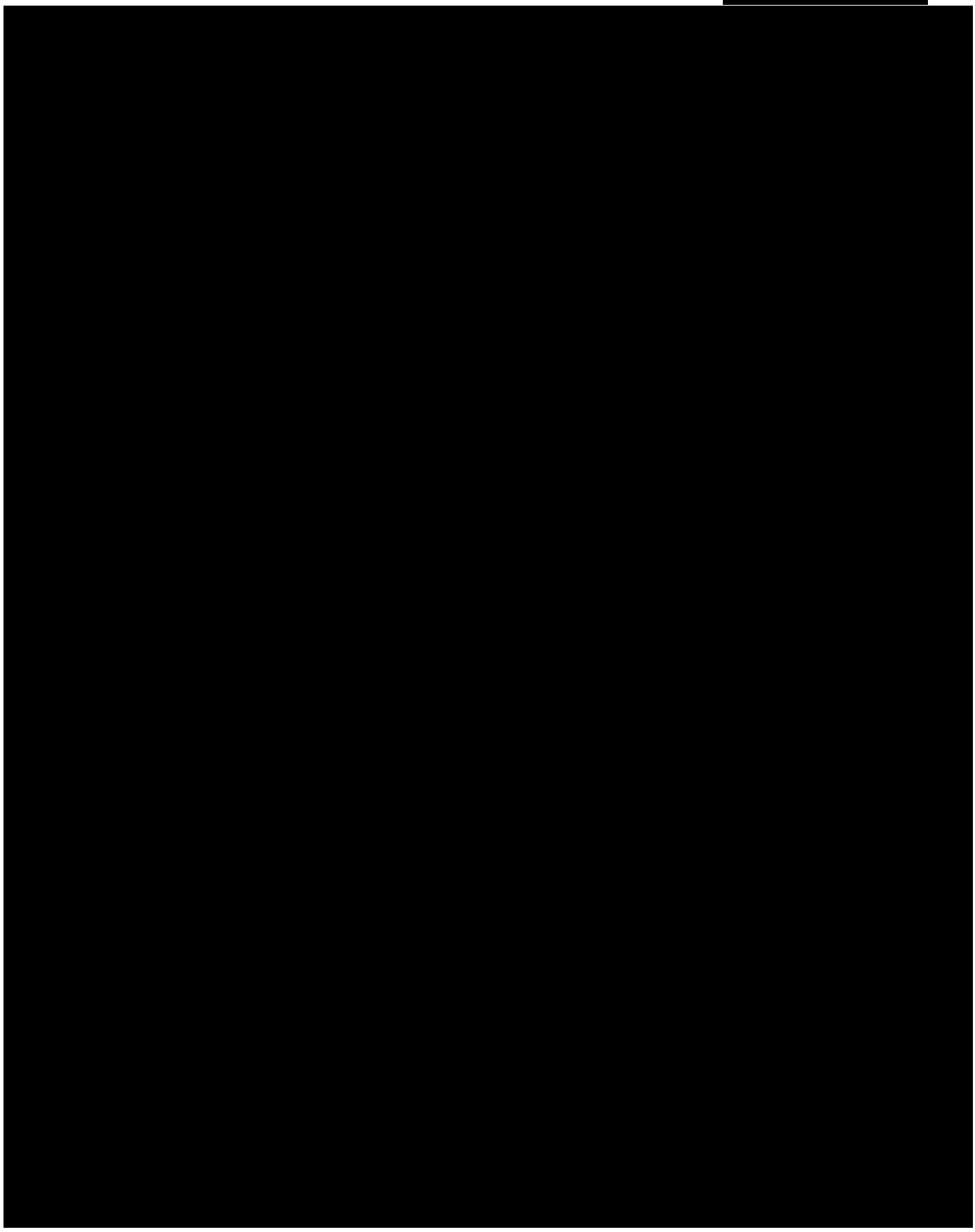
- With methodology in Estimand 1 (Section 2.3.1) using ITT population;

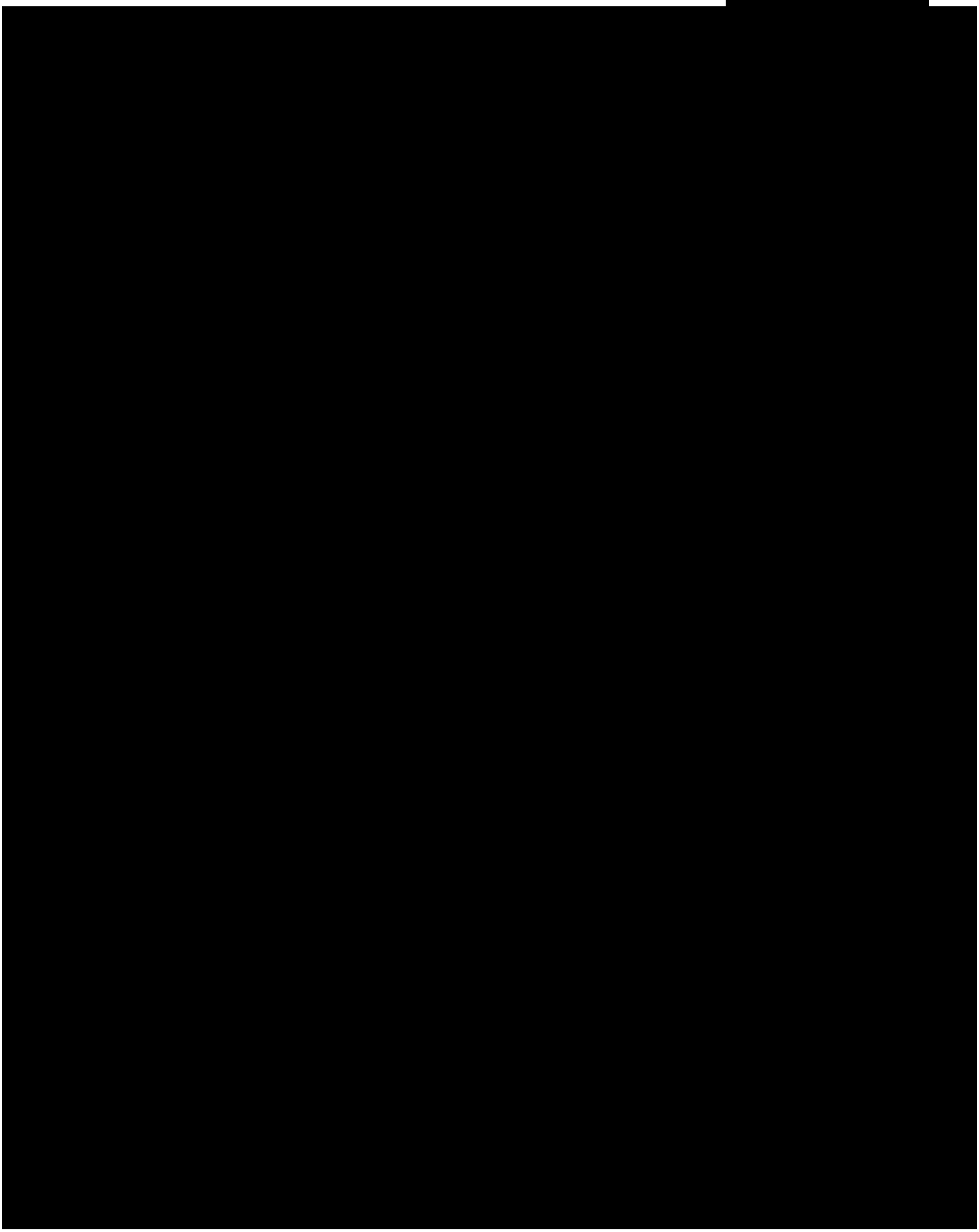
[redacted]

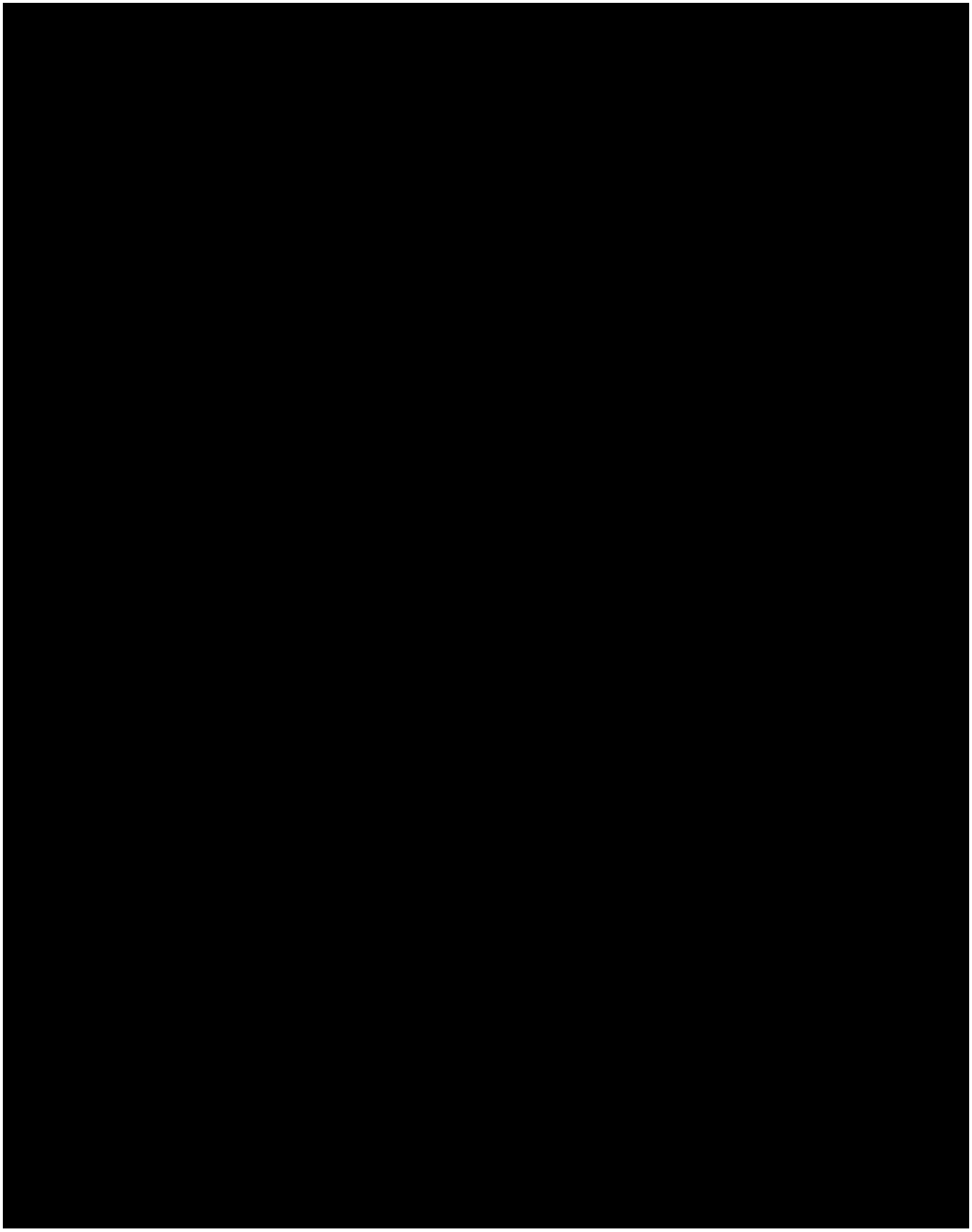
All other secondary efficacy endpoint will be analyzed:

- With methodology in Estimand 1 (Section 2.3.1) using ITT population;

[redacted]







14. Safety Analyses

All safety analyses will be conducted using the Safety population.

14.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the administration of the study intervention in humans, whether or not considered to be related to the study intervention. Any medical condition present prior to informed consent which remains unchanged or improved should not be recorded as an AE at subsequent visits. Any pre-existing medical condition that worsens after first administration of the study intervention will also be considered a new AE. AEs should be documented

from the time the subject provides informed consent until subject participation in the study has been completed. All AEs will be coded using MedDRA Version 25.0.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study intervention is initiated. Only TEAEs will be included in the summary tables by treatment group, but all AEs will be included in the subject listings.

Severity of an AE (mild, moderate, and severe) is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The relationship of each AE (not related, unlikely related, possibly related, and related) to the study intervention and the expectedness of each AE (unexpected and expected) should be determined by the Investigator.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one event for the following: TEAEs, serious TEAEs, serious TEAEs related to study intervention. TEAEs will also be classified by strongest relationship to study intervention (not related, unlikely related, possibly related, or related) and by maximum severity (mild, moderate, or severe). The number and percentage of subjects with a TEAE leading to study intervention discontinuation and with a TEAE leading to death will also be summarized. In addition, similar overall summaries for ocular TEAEs and non-ocular TEAEs will be presented.

Additional TEAE summaries will be produced showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by SOC and PT. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. If a subject reports multiple conditions within the same SOC, that SOC will only be reported once. SOCs and PTs within each SOC will be listed in order of descending frequency for 0.003% AR-15512.

Separate summaries will be provided for the following categories of TEAEs:

- TEAEs
- Ocular TEAEs
- Non-Ocular TEAEs
- Ocular treatment-related TEAEs
- Non-Ocular treatment-related TEAEs
- Serious TEAEs
- Ocular serious TEAEs
- Non-Ocular serious TEAEs
- Ocular TEAEs leading to study intervention discontinuation
- Non-Ocular TEAEs leading to study intervention discontinuation

Summaries of TEAEs by maximum severity and summaries of TEAEs by the strongest relationship to the study intervention will be presented for ocular AEs and non-ocular AEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PTs within each SOC by treatment

group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same SOC or PT within the same SOC, the subject will be counted once under the maximum severity or strongest relationship.

All AEs will be presented in a subject listing. The SAEs, AEs leading to study intervention discontinuation, AEs leading to death will be listed separately.

14.2 Clinical Laboratory Data

Clinical laboratory data including hematology, coagulation, and urinalysis will be collected at Baseline (Day 1), and Day 90 or ET. Overall clinical laboratory results at each visit will be reviewed and be interpretated as normal, abnormal, NCS (non-clinically significant), and abnormal, CS (clinically significant). Abnormal, CS results will be specified.

The actual and change from baseline in laboratory test results will be summarized using continuous descriptive statistics for each treatment group. The interpretation of results relative to the reference range (low panic, low normal, normal, high normal, high panic, abnormal) will be summarized using counts and percentages for each treatment group. Shift tables for the interpretation of results relative to the reference range will be provided comparing baseline with Day 90.

Subject listings of laboratory results (hematology, coagulation, and urinalysis) will be produced. When deemed necessary, manual differential results may be collected, which will be listed in the subject listing for hematology. Urine microscopic results may be collected when abnormal urinalysis results are observed, which will be listed in the subject listing for urinalysis. In addition, the overall laboratory results review and interpretation at each visit will be presented in a separate listing.

14.3 Vital Signs

Vital signs (sitting heart rate in beats/min and sitting blood pressure in mmHg [systolic and diastolic blood pressure]) will be assessed at Screening, Baseline (Day 1), and Day 90 or ET.

The actual and change from baseline in vital signs will be summarized using continuous descriptive statistics by visit for each treatment group. A subject listing of visual acuity will be produced.

14.4 Corrected Visual Acuity

The logarithm of the minimum angle of resolution (logMAR) visual acuity in both eyes will be assessed using an Early Treatment of Diabetic Retinopathy Study (ETDRS) Series 2000 chart at Screening, Baseline (Day 1), and Days 7, 14, 28, 90, or ET.

The actual and change from baseline in logMAR will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics by visit for each treatment group. The actual and changes from baseline to maximum on-treatment value (i.e. the worst on-treatment) will be summarized as well. The maximum on-treatment value is the highest logMAR value for each subject and eye from all post-baseline scheduled or unscheduled visits. In addition, change from baseline categories will be summarized using counts and percentages including the following categories: <= 0, >0 to <=0.09, >= 0.10 to <=0.19, >=0.20 to <=0.29, and >=0.30 for each eye (study eye and fellow eye) by visit and for each treatment group. A subject listing of corrected visual acuity will also be produced.

14.5 Slit-Lamp Biomicroscopy

A slit-lamp biomicroscopy examination of the lids (erythema and edema), conjunctiva (hyperemia and edema), cornea (edema, staining/erosion), anterior chamber (cells, flare), iris, and lens (lens opacity for phakic only), will be performed at Screening, Baseline (Day 1), Days 7, 14, 28, 90, or ET. The findings are graded for clinical significance as clinically significant (CS) and non-clinically significant (NCS).

A shift table of score values will be provided comparing each follow-up visit to the baseline. A subject listing of slit-lamp biomicroscopy will also be produced.

14.6 Intraocular Pressure

Intraocular pressure will be assessed in both eyes at Screening, Baseline (Day 1), Day 90 and ET by a Goldmann applanation tonometer affixed to a slit lamp as preferred device. Results will be taken from a single measurement and will be recorded in mmHg.

The IOP values and changes from baseline for each eye (study eye and fellow eye) will be summarized using continuous descriptive statistics by visit and for each treatment group. A subject listing of IOP will also be produced.

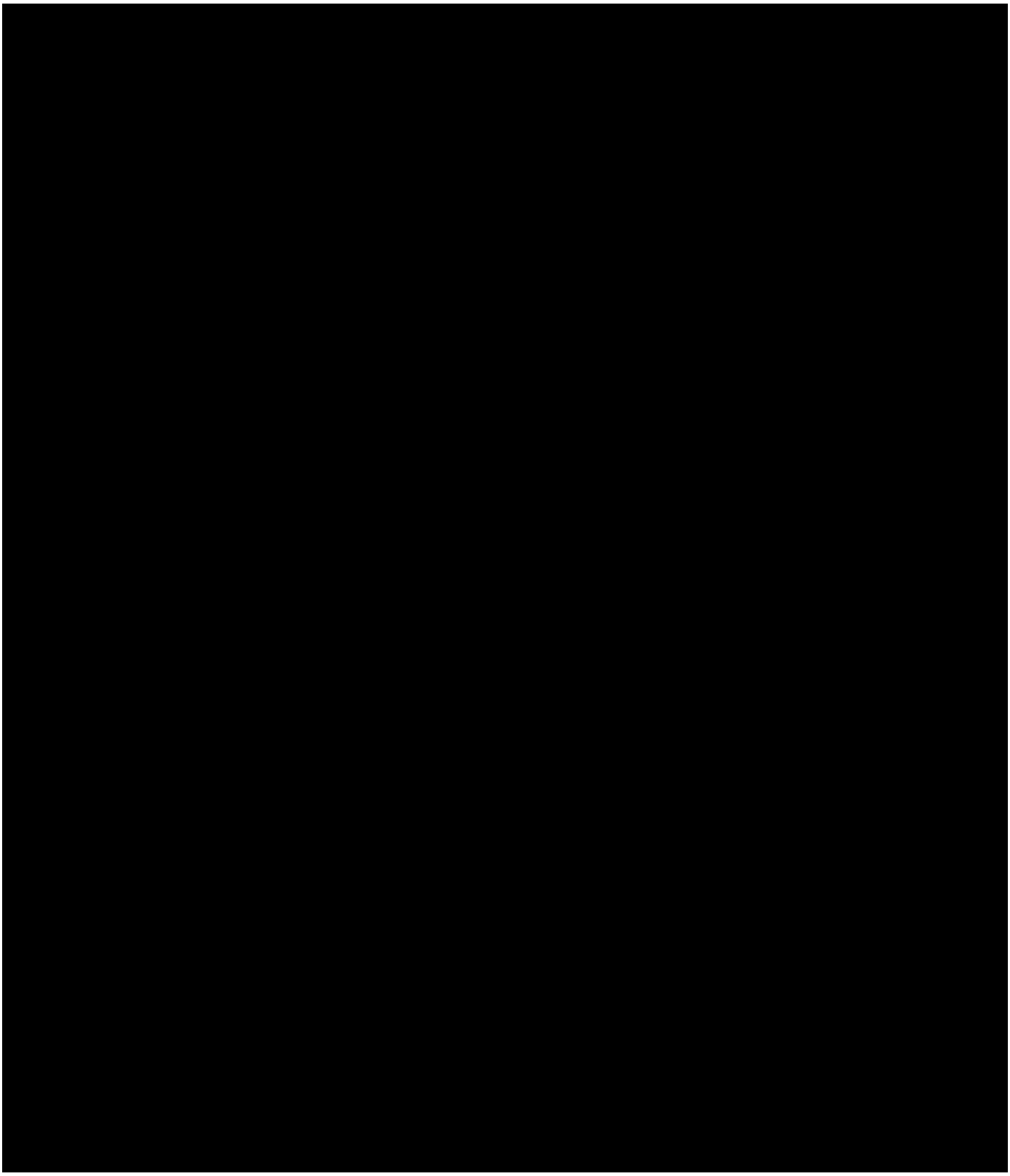
14.7 Dilated Fundus Exam

Dilated fundus exam of vitreous, retina, macula, optic nerve, and choroid will be performed at Screening, Baseline (Day 1), and Day 90 or ET. The results will be graded as normal, abnormal NCS, or abnormal CS.

Shift tables for the dilated fundoscopy parameters will also be provided comparing each follow-up visit to baseline by region, finding, and eye (study eye and fellow eye). A subject listing of the dilated fundoscopy parameters will also be produced.

15. Interim Analyses

No interim analysis is planned for the study.



17. References

1. *ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 05 February 1998.
2. *ICH Harmonised Tripartite Guideline: Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials E9(R1)*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 20 November 2019.
3. *ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports E3*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 30 November 1995.

4. *Schaumberg DA, Gulati A, Mathers WD, Clinch T, Lemp MA, Nelson JD, Foulks GN, Dana R, Development and Validation of a Short Global Dry Eye Symptom Index. 2007. Ocul. Surf. (5:1):50-57.*
5. *PharmaSUG-2013-SP03: Combining Analysis Results from Multiply Imputed Categorical Data.*

[redacted]

19. Tables

Tables that will be included in the topline delivery are shown in boldface font. The topline will be delivered in two batches. Batch 1 tables are shown in boldface font and batch 2 tables are in boldface and italic font.

Table Number	Title	Population
Table 14.1.1	**Subject Disposition**	**All Subjects**
Table 14.1.2.1	**Demographics and Baseline Characteristics**	**Intent-to-Treat Population**
Table 14.1.2.2	Demographics and Baseline Characteristics	Safety Population
Table 14.1.3.1	Ocular Medical History	Safety Population
Table 14.1.3.2	Non-Ocular Medical History	Safety Population
Table 14.1.4.1	Ocular Concomitant Medications	Safety Population
Table 14.1.4.2	Non-Ocular Concomitant Medications	Safety Population
Table 14.1.5.1	Dosing Compliance	Safety Population
Table 14.1.5.2	Treatment Exposure Duration	Safety Population
Table 14.2.1.1	Proportion of Subjects Who Achieved >= 10 mm Increase from Pre-drop at Baseline to Post-drop on Day 14 in Study Eye Unanesthetized Schirmer Score (Estimand 1)	Intent-to-Treat Population

[redacted]

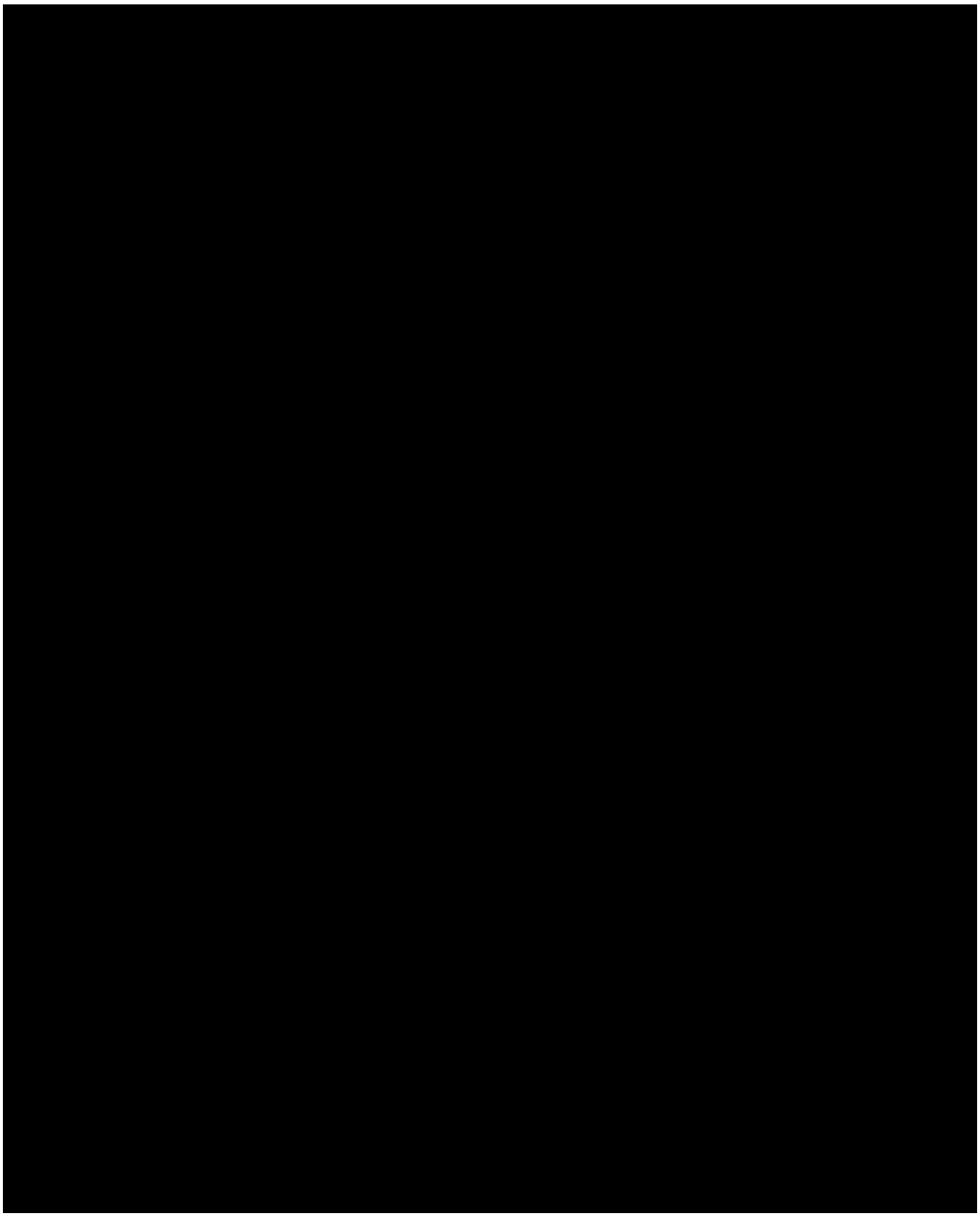
Table Number	Title	Population
[redacted]		
Table 14.2.2.1.1	Change from Baseline in SANDE Score (mm) by Visit (Estimand 1)	Intent-to-Treat Population
[redacted]		
Table 14.2.2.2.1	*Change from Pre-drop at Baseline to Post-drop Unanesthetized Schirmer Score (mm) in Study Eye by Visit (Estimand 1)*	*Intent-to-Treat Population*

Table Number	Title	Population
[redacted]		

Table Number	Title	Population
Table 14.2.2.3.1	Proportion of Subjects Who Achieved >= 10 mm Increase from Pre-drop at Baseline to Post-drop Unanesthetized Schirmer Score in Study Eye by Visit (Estimand 1)	Intent-to-Treat Population

[redacted]

Table Number	Title	Population
[redacted]		
Table 14.2.2.4.1	*Change from Baseline in Eye Dryness Score - Visual Analog Scale (mm) by Visit (Estimand 1)*	*Intent-to-Treat Population*
[redacted]		
Table 14.2.2.5.1	*Change from Baseline in Ocular Discomfort Score - Visual Analog Scale (mm) by Visit (Estimand 1)*	*Intent-to-Treat Population*
[redacted]		



[redacted]

Table 14.3.1.1.1	**Overall Summary of Treatment-Emergent Adverse Events**	**Safety Population**
Table 14.3.1.1.2	**Overall Summary of Ocular Treatment-Emergent Adverse Events**	**Safety Population**
Table 14.3.1.1.3	**Overall Summary of Non-Ocular Treatment-Emergent Adverse Events**	**Safety Population**
Table 14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.2.2	**Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**	**Safety Population**
Table 14.3.1.2.3	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.3.1	Ocular Treatment-Related TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.3.2	Non-Ocular Treatment-Related TEAEs by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.4.1	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population

Table Number	Title	Population
Table 14.3.1.4.2	**Ocular Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term**	**Safety Population**
Table 14.3.1.4.3	Non-Ocular Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.5.1	Ocular Treatment-Emergent Adverse Events Leading to Study Intervention Discontinuation by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.5.2	Non-Ocular Treatment-Emergent Adverse Events Leading to Study Intervention Discontinuation by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.6.1	Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.1.6.2	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.1.7.1	Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Strongest Relationship to Study Intervention	Safety Population
Table 14.3.1.7.2	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Strongest Relationship to Study Intervention	Safety Population
[redacted]		
Table 14.3.2.1.1	Actual and Change from Baseline in Hematology by Visit	Safety Population
Table 14.3.2.1.2	Actual and Change from Baseline in Chemistry by Visit	Safety Population
Table 14.3.2.1.3	Actual and Change from Baseline in Urinalysis by Visit	Safety Population
Table 14.3.2.2.1	Hematology Results by Visit	Safety Population
Table 14.3.2.2.2	Chemistry Results by Visit	Safety Population
Table 14.3.2.2.3	Urinalysis Results by Visit	Safety Population
Table 14.3.2.3.1	Shift in Hematology from Baseline to Day 90	Safety Population
Table 14.3.2.3.2	Shift in Chemistry from Baseline to Day 90	Safety Population

Table Number	Title	Population
Table 14.3.2.3.3	Shift in Urinalysis from Baseline to Day 90	Safety Population
Table 14.3.3	Actual and Change from Baseline in Vital Signs by Visit	Safety Population
Table 14.3.4.1	Actual and Change from Baseline in Corrected Visual Acuity in logMAR Score by Visit	Safety Population
Table 14.3.4.2	Categorical Analysis of Change from Baseline in Corrected Visual Acuity logMAR Score by Visit	Safety Population
Table 14.3.5.1	Shift in Slit-Lamp Biomicroscopy Results by Visit – Study Eye	Safety Population
Table 14.3.5.2	Shift in Slit-Lamp Biomicroscopy Results by Visit – Fellow Eye	Safety Population
Table 14.3.6	Actual and Change from Baseline in Intraocular Pressure (mmHg) by Visit	Safety Population
Table 14.3.7.1	Shift from Baseline in Dilated Fundus Exam Results to Day 90 – Study Eye	Safety Population
Table 14.3.7.2	Shift from Baseline in Dilated Fundus Exam Results to Day 90 – Fellow Eye	Safety Population

20. Listings

Listing Number	Title	Population
Listing 16.1.7.1	Screening, Treatment Randomization, and Investigational Product Assignment	Randomized Subjects
Listing 16.1.7.2	Run-in Administration and Run-in Dispensation	Subjects Who Entered Run-In Period
Listing 16.2.1.1	Subject Disposition	Randomized Subjects
Listing 16.2.1.2	Subject Disposition	Screen Failure Subjects
Listing 16.2.1.3	Informed Consent	All Subjects
Listing 16.2.2.1	Protocol Deviations	Randomized Subjects
Listing 16.2.2.2	Violations of Inclusion/Exclusion Criteria	Randomized Subjects
Listing 16.2.3	Analysis Populations	Randomized Subjects
Listing 16.2.4.1.1	Demographics	Randomized Subjects

Listing Number	Title	Population
Listing 16.2.4.1.2	Childbearing Potential	Female Randomized Subjects
Listing 16.2.4.2.1	Ocular Medical History	Randomized Subjects
Listing 16.2.4.2.2	Non-Ocular Medical History	Randomized Subjects
Listing 16.2.4.3	Prior and Concomitant Medications	Randomized Subjects
Listing 16.2.4.4	Concomitant Procedures	Randomized Subjects
[redacted]		
Listing 16.2.4.6	Controlled Adverse Environment (CAE) Exposure at Screening	Randomized Subjects
[redacted]		
Listing 16.2.5.1	In-Office Study Drug Administration	Randomized Subjects
Listing 16.2.5.2	Study Drug Dispensation	Randomized Subjects
Listing 16.2.5.3	Treatment Kit Accountability	Randomized Subjects
Listing 16.2.6.1	Unanesthetized Schirmer Test	Randomized Subjects
Listing 16.2.6.2	Symptoms Assessment iN Dry Eye (SANDE) Questionnaire	Randomized Subjects
Listing 16.2.6.3	Symptom Questionnaire (Visual Analog Scale)	Randomized Subjects
[redacted]		
Listing 16.2.7.1	Adverse Events	All Subjects
Listing 16.2.7.2	Serious Adverse Events	All Subjects

Listing Number	Title	Population
Listing 16.2.7.3	Adverse Events Leading to Study Intervention Discontinuation	All Subjects
Listing 16.2.7.4	Adverse Events Leading to Death	All Subjects
Listing 16.2.8.1	Hematology and Manual Differential Results	Randomized Subjects
Listing 16.2.8.2	Chemistry	Randomized Subjects
Listing 16.2.8.3	Urinalysis and Urine Microscopic Results	Randomized Subjects
Listing 16.2.8.4	Laboratory Results Review and Interpretation	Randomized Subjects
Listing 16.2.9	Vital Signs	Randomized Subjects
Listing 16.2.10.1	Corrected Visual Acuity	Randomized Subjects
Listing 16.2.10.2	Slit-Lamp Biomicroscopy	Randomized Subjects
Listing 16.2.10.3	Intraocular Pressure	Randomized Subjects
Listing 16.2.10.4	Dilated Fundus Exam	Randomized Subjects
Listing 16.2.11	Urine Pregnancy Test	Female Randomized Subjects
Listing 16.2.12	Unscheduled Visits	Randomized Subjects