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

STUDY ID:

AR-15512-LTSS

STATISTICAL ANALYSIS PLAN

NCT05493111

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Sponsor: Aerie Pharmaceuticals, Inc.

Protocol Number: AR-15512-LTSS

[redacted]

Date: 12MAR2024

Version: 1.0

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SAP Version: 1.0

SAP Date: 12MAR2024

Statistical Analysis Plan Approval

[redacted]

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Statistical Analysis Plan Approval (cont.)

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List of Abbreviations

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
[redacted]	
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BID	*Bis in die* (Twice Daily)
BLQ	Below the Limit of Quantitation
CFB	Change from Baseline
CI	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
DED	Dry Eye Disease
DM	Data Management
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ET	Early Termination
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IRT	Interactive Response Technology
[redacted]	
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
PDF	Portable Document Format
PK	Pharmacokinetic
PT	Preferred Term
[redacted]	
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures
[redacted]	
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe in detail the planned analyses and reporting for protocol AR-15512-LTSS [redacted] 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.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

2. Study Objectives

2.1 Primary Objective

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

2.2 Safety Assessments

- Adverse events (AEs)
- Vital signs (heart rate and blood pressure)
- Endothelial cell counts
- Hematology, chemistry, and urinalysis
- Best corrected visual acuity (BCVA)
- Corrected visual acuity
- Biomicroscopy
- Total ocular staining
- Intraocular pressure (IOP)
- Dilated fundus exam

2.3 Pharmacokinetics Assessment (Selected Sites)

- Systemic exposure in subjects from selected sites (plasma pharmacokinetic [PK] parameters including, but not limited to, $AUC_{0\text{-}t}$, C_{max}, C_{min}, T_{last}, R_{Cmax} and R_{AUC} [where R represents an accumulation factor]).

[redacted]

[redacted]

2.6 Statistical Hypotheses

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

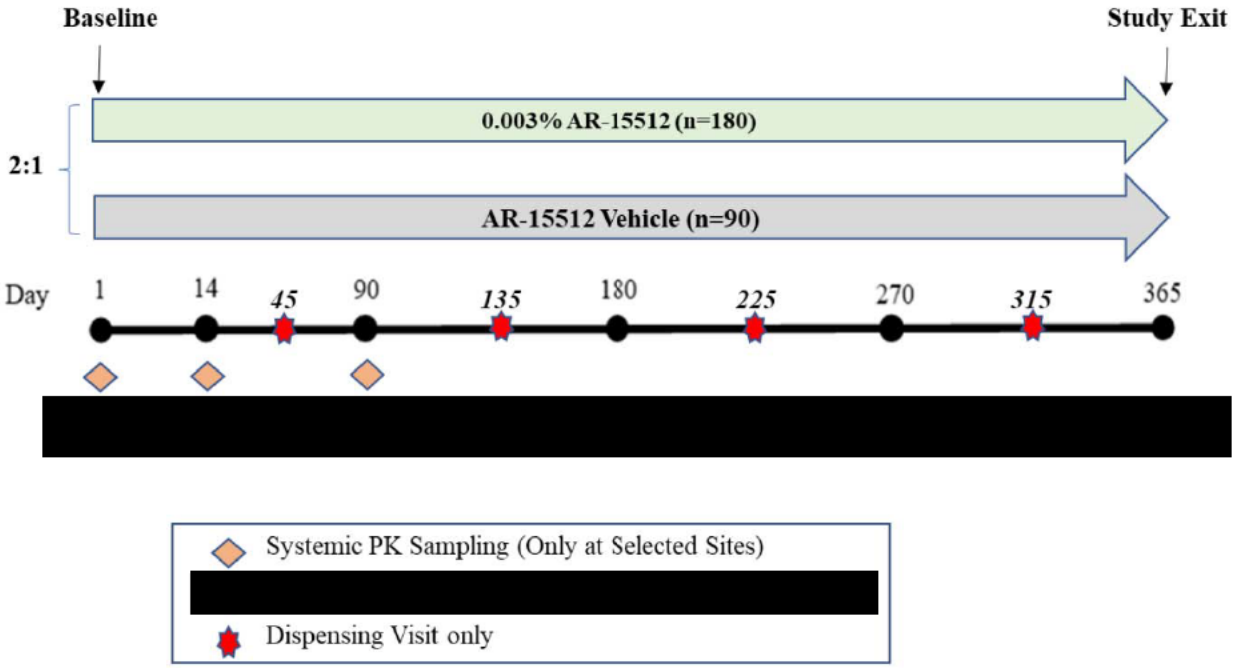
3. Study Design and Procedures

3.1 General Study Design

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

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

Figure 1. Study Design



Scheduled study visits (Days 1, 14, 90, 180, 270, 365) will be referred to as such in all tables and listings to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Dispensing visits (Days 45, 135, 225, 315) will only be presented in listings and not summarized in tables. There is no Day 0; Day 1 is the day of randomization, on which the subjects get 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 event dates before Day 1, study day will be calculated as, (Date of Event) – (Date of First Dose of Study Intervention).

3.2 Schedule of Visits and Assessments

Schedule of visits and procedures is shown in Table 1.

Table 1. Schedule of Visits and Procedures

The following procedures listed in Table 1 including "Pre-drop unanesthetized Schirmer test (at selected sites only)", "At least 30 and up to 45-minute rest period (at selected sites only)", "Pre-drop unanesthetized Schirmer test (at selected sites only)", and "At least 15 and up to 20-minute rest period (at selected sites only)" refer incorrectly to footnote 3. According to Clarification Letter # 1, the correct footnote should be footnote 4.

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

[redacted]

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

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

[redacted]

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

[redacted]

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

All subjects will be centrally assigned to a randomized study intervention using an interactive response technology (IRT). Before the study is initiated, the log-in information and directions for the IRT will be provided to qualified personnel at each site. All qualified subjects will be randomized in a 2:1 ratio within each site to receive 0.003% AR-15512 or AR-15512 vehicle at the Baseline (Day 1) visit. The IRT will provide the site with the specific kit number(s) for each randomized subject at the time of randomization. Sites will dispense the study intervention according to the IRT instructions and the Schedule of Visits and Assessments 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 subject 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 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 study, the investigator and site staff performing eligibility, safety, PK [redacted] assessments and the subjects will be masked. Subjects will be informed that there is a 1 in 3 chance they will receive vehicle. AR-15512 (0.003%) and AR-15512 vehicle will be provided in identical, single-use, blow-fill-seal containers.

A randomization schedule for allocating the study interventions within a site will be prepared by an unmasked statistician who is not involved in the day-to-day conduct of the study. The Sponsor clinical study team (e.g., personnel involved in day-to-day study management, monitors, data managers, and statisticians) will be masked.

4.2.2 UNMASKING

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. The Medical Monitor will decide whether the study intervention for the subject should be unmasked. The study intervention

assignment will be revealed on a subject-by-subject basis, thus leaving the masking on the remaining subjects intact.

5. Sample Size and Power Considerations

This is a phase 3 study to determine the long-term safety of 0.003% AR-15512. Approximately 270 subjects will be randomized in a 2:1 randomization ratio to receive 0.003% AR-15512 (180 subjects) or AR-15512 vehicle (90 subjects). Assuming a dropout rate of 40%, approximately 108 subjects randomized to receive 0.003% and 54 subjects randomized to receive vehicle are expected to reach the Day 365 visit.

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

6. Data Preparation

6.1 Input Data

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

- Central laboratory data [redacted] (hematology, chemistry, urinalysis, PK)

Database locks are planned after all subjects have completed the Day 365 visit (i.e., 12 months) or exited the study.

When all prerequisites for a database lock have been met, including availability of all masked external data, the database will be locked. Following each 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 Ora.

The final analyses will be carried out after the following have occurred:

- Respective database lock has occurred, including receipt of all final versions of external vendor data for the appropriate period, with written authorization provided by appropriate Ora 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 Ora 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 ADaM-formatted data. The SDTM and ADaM model versions, implementation guide versions, Pinnacle 21 version will be documented in the respective reviewer's guides in the final CDISC package. Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model or above.

7. Analysis Populations

7.1 Safety

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

[redacted]

7.4 PK Population

All subjects in the Safety Population who have at least one measurable PK concentration will be included in the PK Population. All PK analyses will be based on the PK Population.

8. General Statistical Considerations

8.1 Unit of Analysis

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

8.2 Study Eye Selection

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

[redacted].

8.3 Missing or Inconclusive Data Handling

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

Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study intervention and the end date is missing, or on/after the first dose of study intervention, in which case missing day will be imputed as the first dose day of study intervention.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study intervention and the end date is missing, or on/after the first dose of study intervention, in which case missing day and month will be imputed as the first dose day and month of study intervention.
- Completely missing dates will be imputed as the first dose date of study intervention unless the end date is on or before the first dose date of study intervention, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study intervention and the start date is on or before the last dose of study intervention, in which case missing day will be imputed as the last dose day of study intervention.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study intervention and the start date is on or before the last dose of study intervention, in which case missing day and month will be imputed as the last dose day and month of study intervention.
- Completely missing dates will not be imputed.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

8.4 Definition of Baseline

Baseline is the measure at Baseline (Day 1) visit.

[redacted]

8.5 Data Analysis Conventions

All data analysis will be performed by Ora. 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, standard deviation (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 (CFB) will be calculated as, Post-Baseline Result – Baseline Result, 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 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) 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". All odds ratios or 95% CI values less than 0.001 will be presented as "<0.001" and values greater than 999.999 will be presented as ">999.999".

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

10. Multicenter Consideration

All individual investigative sites with less than 10 randomized subjects may be pooled into one analysis center for exploratory efficacy analyses.

11. 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, enrolled, and randomized will be presented. Enrolled subjects are those who signed informed consent, met all eligibility criteria, but may or may not be randomized. Provided that subjects may be rescreened once after initial screen failure, each subject will be reported based on his/her final enrollment status, e.g. screen failure, randomized.

The number and percentages of subjects in each analysis population [redacted] Safety, and PK) will be presented.

The number and percentages of subjects who completed the study or discontinued from the study will be presented; ongoing subjects will be presented for any summaries completed prior to the final database lock. The reasons for study discontinuation to be summarized will include AE, withdrawal of consent, non-compliance, lost to follow-up, disallowed concurrent treatment, pregnancy, 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 will be provided that include subject disposition for randomized subjects and screen failed subjects separately, informed consent, violation of inclusion/exclusion criteria, protocol deviations, and analysis populations. In addition, details of the study randomization, including randomization date and time, randomized treatment, actual treatment will also be included in a subject listing.

12. Demographic and Baseline Characteristics

12.1 Demographic Variables

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 in the summary table, but all races as collected will be presented in the listing. Iris color will be summarized at the subject level for right eye and left eye separately. Demographic variables will be summarized using Safety Population.

Age (years) will be summarized, for all subjects and by treatment group, using continuous descriptive statistics. Age will also be categorized as follows: 18-29, 30-45 years, 46-60 years, 61-75 years, and >75 years. The number and percentage of subjects will be presented, for all subjects and by treatment group, for age category, sex assigned at birth, race, ethnicity, and iris color of each 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]

13. Medical History and Concomitant Medications

13.1 Medical History

Medical history will be obtained at the Baseline (Day 1) 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, for all subjects and by treatment group, at the subject level by System Organ Class (SOC) and Preferred Term (PT). 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.

13.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global (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 they report 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 0.003% AR-15512 subjects.

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

13.3 Concomitant Procedures

Concomitant procedures will be coded using MedDRA Version 25.0. Concomitant procedures will be listed but not summarized.

14. Dosing Compliance and Treatment Exposure

14.1 Dosing Compliance

At all visits, the morning dose of randomized study intervention will be administered by the site staff. All other doses will be administered by the subject.

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

Overall study intervention dosing compliance (% compliance) starting from Baseline (Day 1) to Day 365 (or ET visit) will be assessed by:

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

The overall compliance will be calculated for any subject who has received at least one dose of study intervention. The overall compliance may not be calculated for subjects who have erroneous data entries.

The number of actual doses received will be:

Number of Actual Doses Received = Total Number of Dispensed Vials - Total Number of Unused Vials Returned

Where the Total Number of Unused Vials Returned is the sum of "Number of Vials Unused" as recorded on Treatment Kit Accountability Log starting from Baseline (Day 1) and until Study Exit (Day 365 or ET visit). For subjects who have their in-office dose administered on the Day 365 visit, 1 will be added to the Number of Actual Doses Received. This is because the in-office dosing on Day 365, using a vial taken from the Day 315 kit, will occur after the Treatment Kit Accountability Log for the Day 315 kit is completed, therefore the last used vial would otherwise not be counted in the Treatment Kit Accountability Log.

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 is only one morning dose scheduled on the Day 365 visit. The date of last dose is the latest non-missing dosing date

collected on the Study Exit 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. Subject listings of in-office study drug dispensation, treatment kit accountability, and in-office study drug instillation will be provided.

14.2 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 Exit eCRF page or the Study Drug Administration eCRF page, and the date of first dose is collected on the Study Drug Administration eCRF page.

15. Safety Analyses

All safety analyses will be conducted using the Safety Population.

15.1 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 reported 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 them 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, expected, and not applicable) 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 related to study intervention include possibly related or related TEAEs. 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 subjects.

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.

[redacted]

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

15.2 Vital Signs

Vital signs (sitting heart rate in beats/min, sitting blood pressure in mmHg [systolic and diastolic]) will be assessed at Baseline (Day 1), on Days 14, 90, 180, and 270, and 365 or ET visit.

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 vital signs will be produced.

15.3 Endothelial Cell Counts

Specular microscopy of the central cornea will be performed at Baseline (Day 1) and on Day 365 or ET visit. Three images of the central corneal endothelium will be taken at each of the specified visits for each eye. Average cell density for each image will be generated by a built-in algorithm and recorded in the eCRFs. The overall average cell density of the central corneal endothelium will be calculated by the EDC system and summarized. The actual and change from baseline in overall average cell density will be summarized for each eye (right eye and left eye) using continuous descriptive statistics by visit for each treatment group. The presence or absence of abnormal cellular morphology (polymegethism) will be determined by visual inspection of images, noted in the eCRF, and presented in the subject listing of endothelial cell count. In addition, number and percentage of subjects with 10% or more decrease in overall average cell density from baseline to study exit visit, number and percentage of subjects having polymegethism at study exit and normal (i.e. absence of polymegethism) at baseline will be summarized separately and presented in separately listings.

15.4 Clinical Laboratory Data

Clinical laboratory data including hematology, chemistry, and urinalysis will be collected at Baseline (Day 1), on Day 180, and on Day 365 or ET visit. Overall clinical laboratory results at each visit will be reviewed and be interpretated as Normal; Abnormal, non-clinically significant (NCS); and Abnormal, clinically significant (CS). Abnormal, CS results will be specified. Clinical laboratory values (other than pregnancy tests results) that are noted as abnormal, CS at study exit and that are changes from Screening values will be documented as AEs.

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 to baseline.

Subject listings of laboratory results (hematology, chemistry, 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.

15.5 Best Corrected Visual Acuity

Best corrected visual acuity in both eyes will only be performed at Baseline (Day 1) and on Day 365 or ET visit and will be assessed by an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. The actual and change from baseline in final BCVA letter score for each eye (right eye and left eye) will be summarized using continuous descriptive statistics by visit for each treatment group. In addition, change from baseline categories will be summarized using counts and percentages for each eye (right eye and left eye) by visit and for each treatment group in the following categories:

- <= -15
- >= -14 to <= -10
- >= -9 to <= -5
- >= -4 to <0
- >= 0

A subject listing of BCVA will be produced.

15.6 Corrected Visual Acuity

Logarithmic minimum angle of resolution (logMAR) visual acuity in both eyes will be assessed using an ETDRS Series 2000 chart at Baseline (Day 1), on Days 14, 90, 180, and 270, and on Day 365 or ET visit.

The actual and change from baseline in logMAR will be summarized for each eye (right eye and left eye) using continuous descriptive statistics by visit for each treatment group. In addition, change from baseline categories will be summarized using counts and percentages for each eye (right eye and left eye) by visit and for each treatment group in the following categories:

- <= 0
- >0 to <=0.09
- >= 0.10 to <=0.19
- >=0.20 to <=0.29
- >=0.30

A subject listing of corrected visual acuity will also be produced.

15.7 Biomicroscopy

A slit-lamp biomicroscopy examination of the lid (erythema, edema), conjunctiva (hyperemia and edema), cornea (edema, staining/erosion), anterior chamber (cells, flare), iris, lens (lens status and lens opacity

[phakic only]) and anterior vitreous will be performed in both eyes at Baseline (Day 1), on Days 14, 90, 180, and 270 and on Day 365 or ET visit. The findings are graded for clinical significance as non-clinically significant (NCS) and clinically significant (CS).

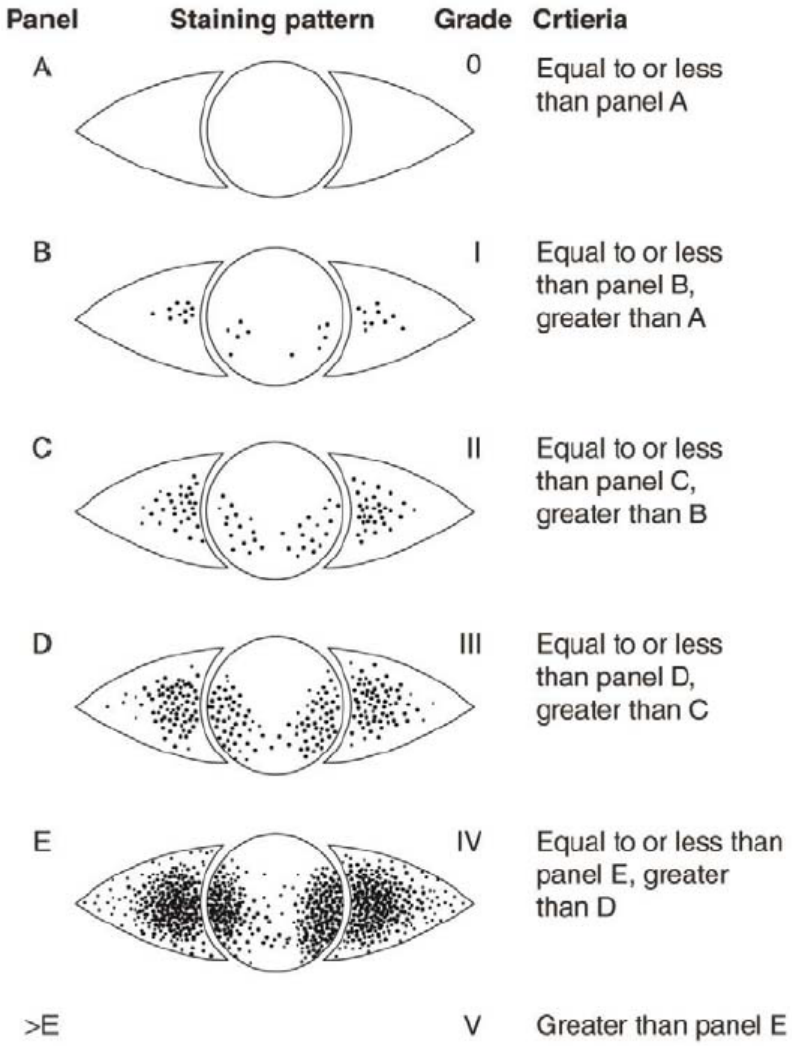
A shift table of numeric score results will be provided comparing each follow-up visit to the baseline for each eye (right eye and left eye) by visit for each treatment group. Additionally, discrete summaries will be provided by region, finding, visit, and eye (right eye and left eye) for the number of subjects with clinically significant biomicroscopy findings as determined by the Investigator. A subject listing of slit-lamp biomicroscopy will also be produced.

15.8 Total Ocular Staining

Ocular surface staining will be performed at Baseline (Day 1), on Days 14, 90, 180, and 270, and 365 or ET visit starting from right eye and followed by left eye. Sodium fluorescein staining of the cornea and lissamine green staining of conjunctiva will be performed based on Oxford grading scheme on a scale of 0 to 5 with half (0.5) grade increments used, as shown in Figure 2. Total ocular staining is then reported in eCRF as the sum of total corneal staining (0-5) and total conjunctival staining (0-10) for a maximum possible score of 15 per eye.

The actual and change from baseline in total corneal staining, total conjunctival staining, and total ocular staining score will be summarized for each eye (right eye and left eye) using continuous descriptive statistics by visit for each treatment group. A subject listing of total ocular staining will also be produced.

Figure 2. Oxford Grading Scheme for Ocular Staining



15.9 Intraocular Pressure (IOP)

The IOP will be assessed in both eyes at Baseline (Day 1), on Days 14, 90, 180, 270, and 365 or ET visit by a Goldmann applanation tonometer affixed to a slit lamp as the preferred device. Results will be taken from a single measurement and will be recorded in mmHg.

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

15.10 Dilated Fundus Exam

Dilated fundus exam of the vitreous, retina, macula, choroid, and optic nerve will be performed at Baseline (Day 1), on Days 14, 90, 180, 270, and 365 or ET visit. 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 eye (right eye and left eye), region, and result. A subject listing of the dilated fundoscopy parameters will also be produced.

16. Pharmacokinetics Analysis

Blood draw for systemic PK measures will be performed at selected sites to include approximately 35 subjects (i.e., expected to yield approximately 20 subjects exposed to 0.003% AR-15512 and 10 subjects exposed to AR-15512 vehicle). Samples collected from subjects will be analyzed for AR-15512 concentration. Six blood samples per visit will be collected on Day 1, Day 14, and Day 90. On these visits, one PK sample will be collected pre-dose and 5 samples will be collected post-dose at the scheduled time points 15 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours. Actual sampling times will be recorded. Unscheduled time points during the visit may be collected and the actual time of collections will be recorded.

AR-15512 concentrations will be listed and summarized at each scheduled time point of each visit for each treatment group. The summary will consist of the number of subjects (n), geometric mean, arithmetic mean, SD, arithmetic coefficient of variation (CV), minimum, median, maximum, and the 25th (Q1) and 75th (Q3) percentiles, Summary statistics will be reported to 3 significant figures except CV (%), which will be reported to 1 decimal place (e.g., XX.X%). For the purpose of concentration reporting and PK parameter generation, values below the limit of quantitation (BLQ) that occur prior to the time point with the first measurable concentration will be treated as 0.0. All other BLQ values will be treated as missing. The individual subject concentrations will be plotted versus actual sampling times on both linear/linear and log/linear (i.e., semi-log) scales. The mean concentrations will be plotted versus the nominal sampling times on linear/linear and semi-log scales.

PK parameters will be estimated from the individual subject plasma concentration versus time data by applying a non-compartmental approach using Phoenix WinNonlin® v8.3 (Certara, Princeton, NJ) or higher. Actual rather than nominal sampling times will be used for the calculation of PK parameters. Where the data allow, the PK parameters as described on Table 2 will be calculated.

Table 2. Pharmacokinetic Parameters

Parameters Estimated	Parameter Description	Parameter Unit
C_{max}	Maximum plasma concentration	ng/mL or µg/mL
C_{min}	Minimum plasma concentration	ng/mL or µg/mL
T_{max}	Time of observed maximum concentration	hr
T_{last}	Time point with the last measurable concentration	hr
AUC_{0-t}	Area under the plasma concentration - time curve (AUC) from 0 hour to the time of the last quantifiable concentration, using the linear up/log down trapezoidal rule	hr*ng/mL or hr*µg/mL
R_{Cmax}	Accumulation ratio based on C_{max}	N/A
R_{AUC}	Accumulation ratio based on AUC_{0-t}	N/A

Note: R_{Cmax} and R_{AUC} values will be calculated as the Day 14 or Day 90 C_{max}/Day 1 C_{max} or Day 14 or Day 90 AUC_{0-t} /Day 1 AUC_{0-t} as appropriate.

The AUC parameters will not be generated unless there are at least three (3) measurable AR-15512 concentrations in the PK profile. If parameters based on the terminal phase are reported, they will only be reported if the goodness-of-fit parameter, R^2, is greater than 0.9 and the percent of AUC extrapolated to time infinity ($AUC_{\%extrap}$) is less than 20%. Accumulation after repeat dosing will be assessed by calculating Day 14 and Day 90 accumulation ratios based on the exposure parameters C_{max} and AUC_{0-t}. They will be calculated as:

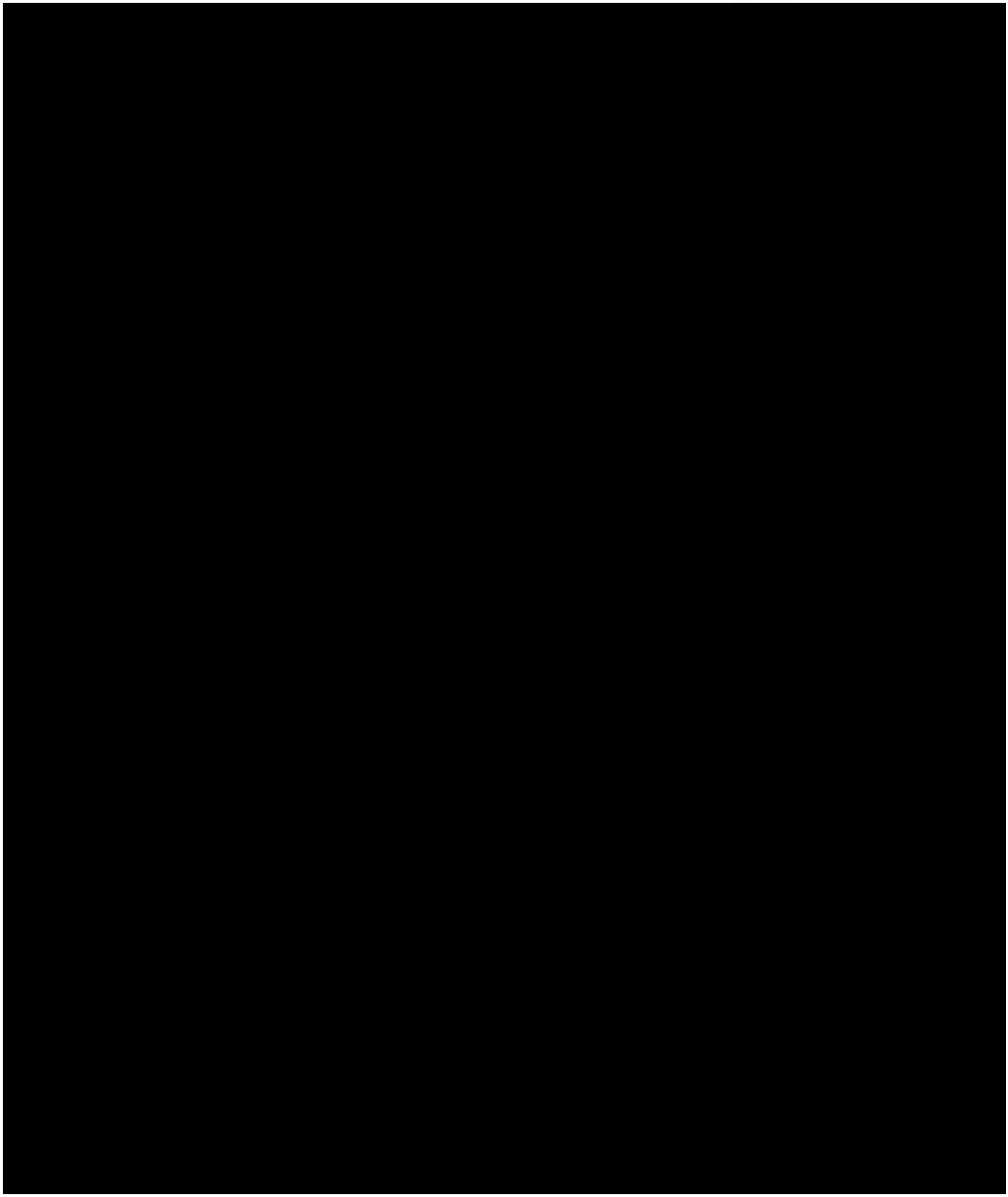
Day 14 or 90 C_{max}/Day 1 C_{max}

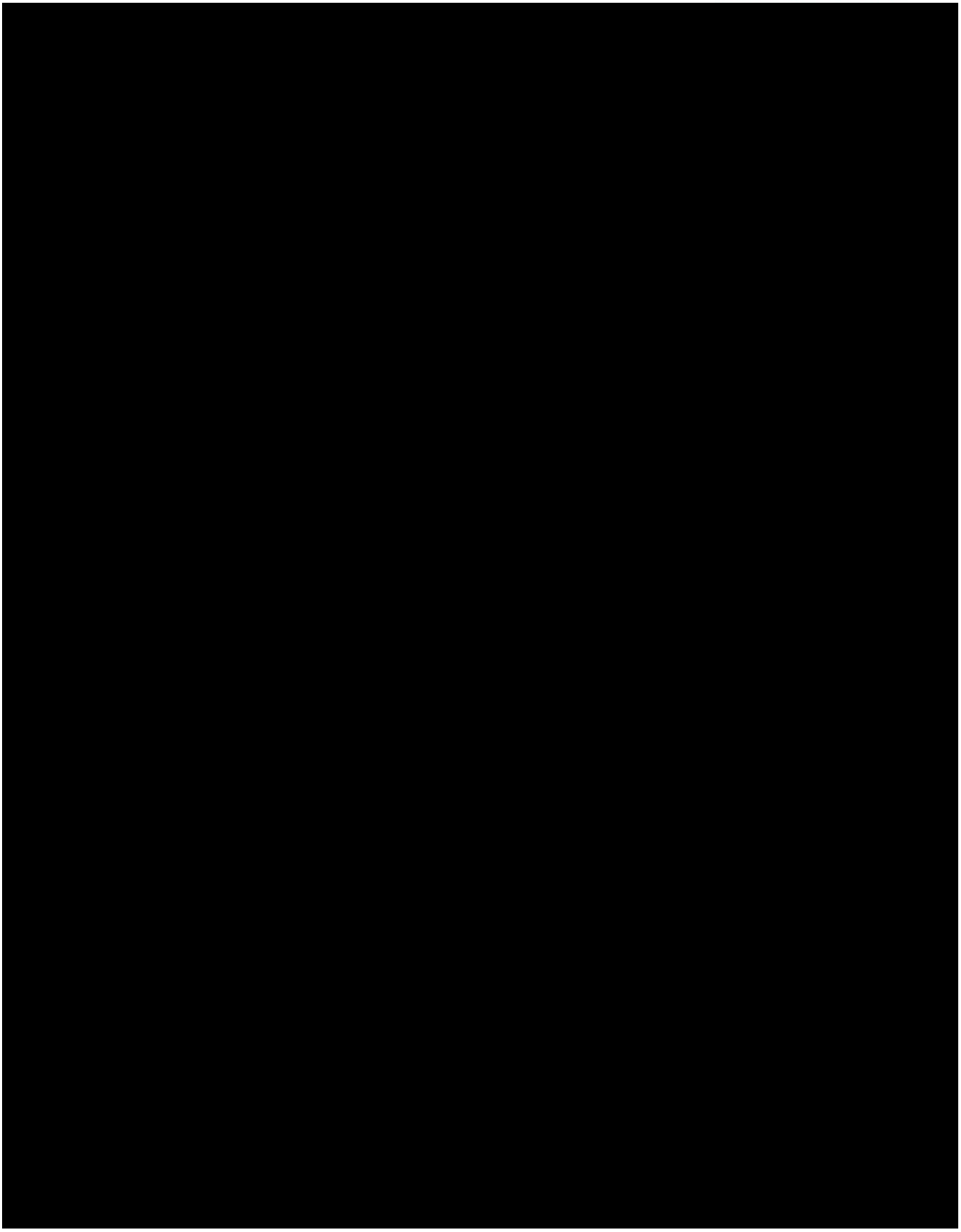
Day 14 or 90 AUC_{0-t}/Day 1 AUC_{0-t}.

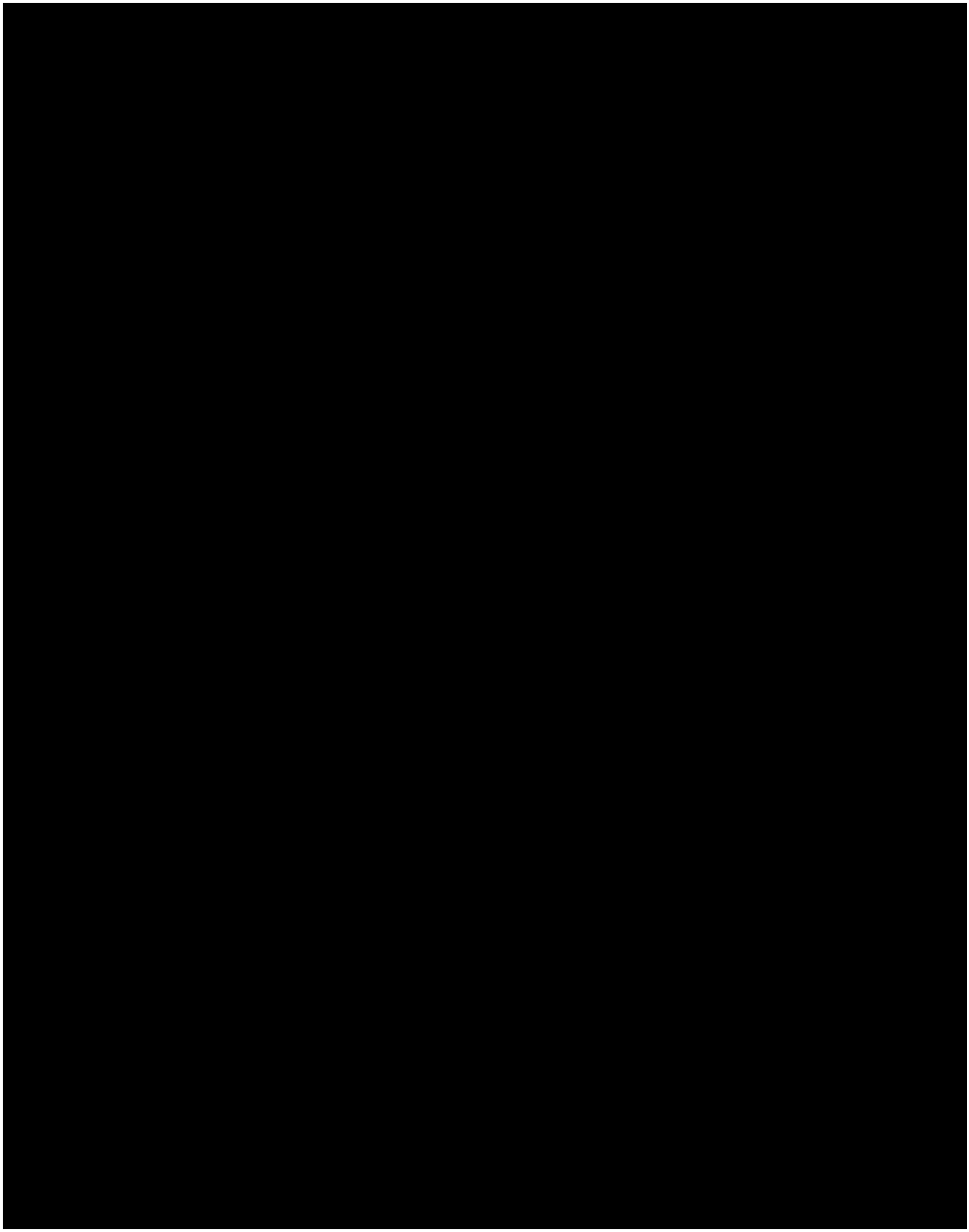
All PK parameters will be reported to three significant figures. Continuous parameters such as C_{max}, C_{min}, and AUC_{0-t} will be summarized using continuous descriptive statistics including number of subjects (n), geometric mean, arithmetic mean, SD, arithmetic CV, minimum, median, maximum, Q1 and Q3. Discrete parameters such as T_{max} and T_{last} will be summarized as n, minimum, median, and maximum only.

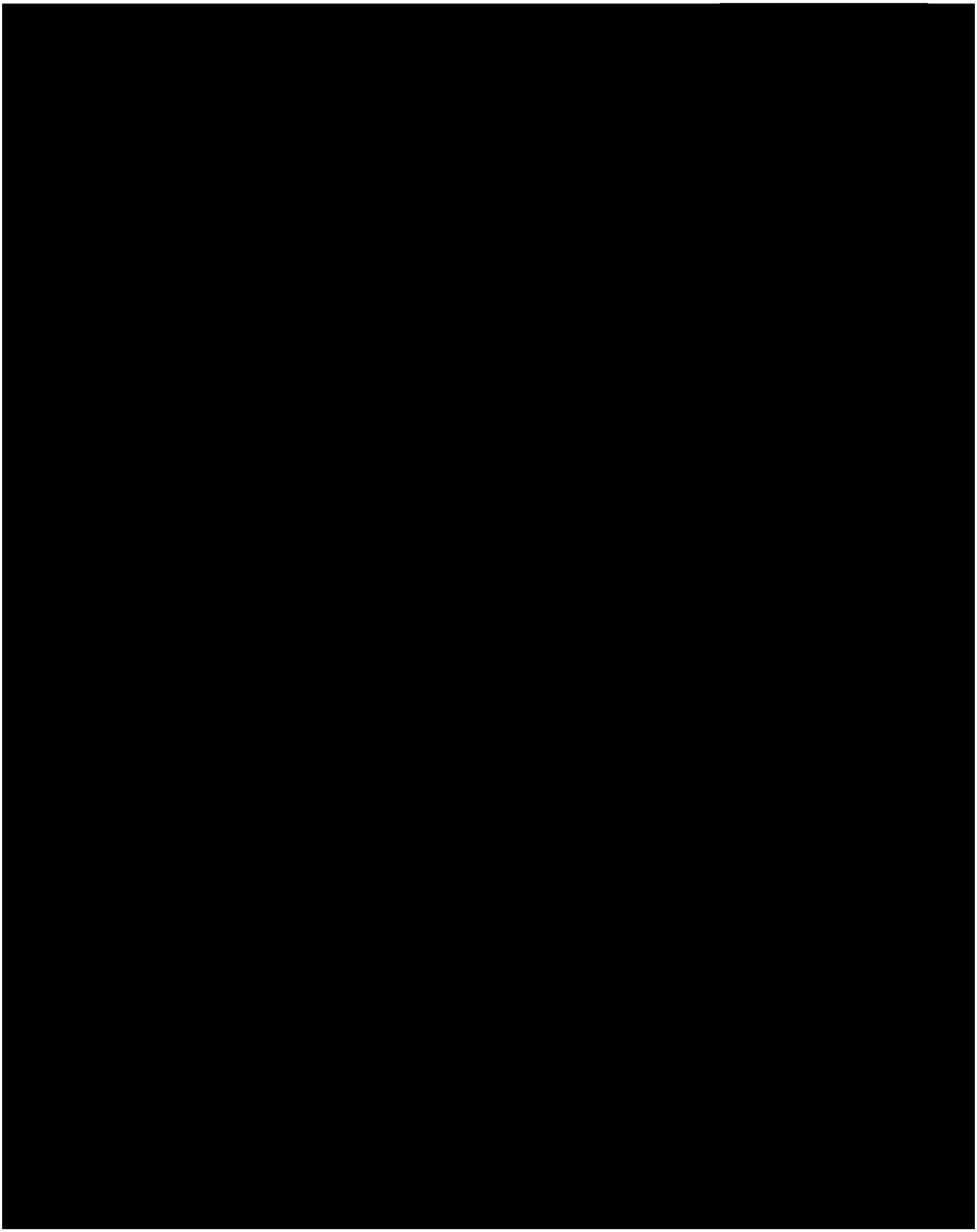
When more than half of the samples at a given timepoint for a given treatment group are BLQ, no summation of the concentrations and PK parameter derivation will be performed.

[redacted]









20. 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: Structure and Content of Clinical Study Reports E3*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 30 November 1995.

21. Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

22. Tables

No topline is planned for the final analysis.

Table Number	Title	Population
Table 14.1.1	Subject Disposition	All Subjects
Table 14.1.2	Demographics and Baseline Characteristics	Safety Population
Table 14.1.3.1	Ocular Medical History	Safety Population

Table Number	Title	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

[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 Number	Title	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 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	Actual and Change from Baseline in Vital Signs by Visit	Safety Population
Table 14.3.3.1	Actual and Change from Baseline in Overall Average Endothelial Cell Density by Visit	Safety Population
Table 14.3.3.2	Number and Percentage of Subjects with 10% or More Decrease from Baseline to Study Exit in Overall Average Endothelial Cell Density	Safety Population
Table 14.3.3.3	Number and Percentage of Subjects having Polymegethism at Study Exit and Normal at Baseline	Safety Population
Table 14.3.4.1.1	Actual and Change from Baseline in Hematology by Visit	Safety Population
Table 14.3.4.1.2	Actual and Change from Baseline in Chemistry by Visit	Safety Population
Table 14.3.4.1.3	Actual and Change from Baseline in Urinalysis by Visit	Safety Population
Table 14.3.4.2.1	Hematology Results by Visit	Safety Population
Table 14.3.4.2.2	Chemistry Results by Visit	Safety Population
Table 14.3.4.2.3	Urinalysis Results by Visit	Safety Population
Table 14.3.4.3.1	Shift in Hematology from Baseline by Visit	Safety Population
Table 14.3.4.3.2	Shift in Chemistry from Baseline by Visit	Safety Population
Table 14.3.4.3.3	Shift in Urinalysis from Baseline by Visit	Safety Population

Table Number	Title	Population
Table 14.3.5.1	Actual and Change from Baseline in Best Corrected Visual Acuity Letter Score by Visit	Safety Population
Table 14.3.5.2	Categorical Analysis of Change from Baseline in Best Corrected Visual Acuity Letter Score by Visit	Safety Population
Table 14.3.6.1	Actual and Change from Baseline in Corrected Visual Acuity in logMAR Score by Visit	Safety Population
Table 14.3.6.2	Categorical Analysis of Change from Baseline in Corrected Visual Acuity logMAR Score by Visit	Safety Population
Table 14.3.7.1	Shift in Slit-Lamp Biomicroscopy Results by Visit – Right Eye	Safety Population
Table 14.3.7.2	Shift in Slit-Lamp Biomicroscopy Results by Visit – Left Eye	Safety Population
Table 14.3.7.3	Number and Percentage of Subjects with Clinically Significant Biomicroscopy Findings as Determined by the Investigator	Safety Population
Table 14.3.8	Actual and Change from Baseline in Ocular Surface Staining Score by Visit	Safety Population
Table 14.3.9	Actual and Change from Baseline in Intraocular Pressure (mmHg) by Visit	Safety Population
Table 14.3.10.1	Shift from Baseline in Dilated Fundus Exam Results by Visit – Right Eye	Safety Population
Table 14.3.10.2	Shift from Baseline in Dilated Fundus Exam Results by Visit – Left Eye	Safety Population
Table 14.3.11.1	Plasma Concentrations (ng/mL) of AR-15512 by Visit	Pharmacokinetic Population
Table 14.3.11.2	Pharmacokinetic Parameters of AR-15512 by Visit	Pharmacokinetic Population

[redacted]

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23. Listings

Listing Number	Title	Population
Listing 16.1.7	Screening, Treatment Randomization, and Investigational Product Assignment	Randomized Subjects
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 16.2.4.1.2	Childbearing Potential	Female Randomized Subjects
[redacted]		
Listing 16.2.4.3.1	Ocular Medical History	Randomized Subjects
Listing 16.2.4.3.2	Non-Ocular Medical History	Randomized Subjects
Listing 16.2.4.4	Prior and Concomitant Medications	Randomized Subjects
Listing 16.2.4.5	Concomitant Procedures	Randomized Subjects
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
[redacted]		
Listing 16.2.7.1	Adverse Events	All Subjects
Listing 16.2.7.2	Serious Adverse Events	All Subjects
Listing 16.2.7.3	Adverse Events Leading to Study Intervention Discontinuation	All Subjects

Listing Number	Title	Population
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	Endothelial Cell Counts	Randomized Subjects
Listing 16.2.10.2	Endothelial Cell Counts for Subjects with 10% or More Decrease from Baseline to Study Exit in Overall Average Cell Density	Randomized Subjects
Listing 16.2.10.3	Endothelial Cell Counts for Subjects having Polymegethism at Study Exit and Normal at Baseline	Randomized Subjects
Listing 16.2.11	Best Corrected Visual Acuity (BCVA)	Randomized Subjects
Listing 16.2.12	Corrected Visual Acuity	Randomized Subjects
Listing 16.2.13	Slit-Lamp Biomicroscopy	Randomized Subjects
Listing 16.2.14	Ocular Surface Staining	Randomized Subjects
Listing 16.2.15	Intraocular Pressure	Randomized Subjects
Listing 16.2.16	Dilated Fundus Exam	Randomized Subjects
Listing 16.2.17.1	Plasma Concentrations of AR-15512	Randomized Subjects
Listing 16.2.17.2	Pharmacokinetic Parameters of AR-15512	Randomized Subjects
[redacted]		
Listing 16.2.19	Urine Pregnancy Test	Female Randomized Subjects
Listing 16.2.20	Unscheduled Visits	Randomized Subjects

24. Figures

Figure Number	Title	Population
[redacted]		
Figure 14.3.2.1	Mean (+/- SD) Plasma Concentrations of AR-15512 by Visit	Pharmacokinetic Population
Figure 14.3.2.2	Mean (+/- SD) Plasma Concentrations of AR-15512 by Visit (Semi-log Scale)	Pharmacokinetic Population
Figure 14.3.2.3	Individual Plasma Concentrations of AR-15512 by Subject	Pharmacokinetic Population
Figure 14.3.2.4	Individual Plasma Concentrations of AR-15512 by Subject (Semi-log Scale)	Pharmacokinetic Population