A Phase 3b Study to Investigate the Effect of 0.003% AR-15512 on the Ocular Surface Characteristics of Subjects with Dry Eye Disease

STUDY ID

DEF512-E003

STATISTICAL ANALYSIS PLAN v 1.0

April 22, 2025

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1. TITLE PAGE

A Phase 3b Study to Investigate the Effect of 0.003% AR-15512 on the Ocular Surface Characteristics of Subjects with Dry Eye Disease

Sponsor:	Alcon Research, LLC and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099 USA
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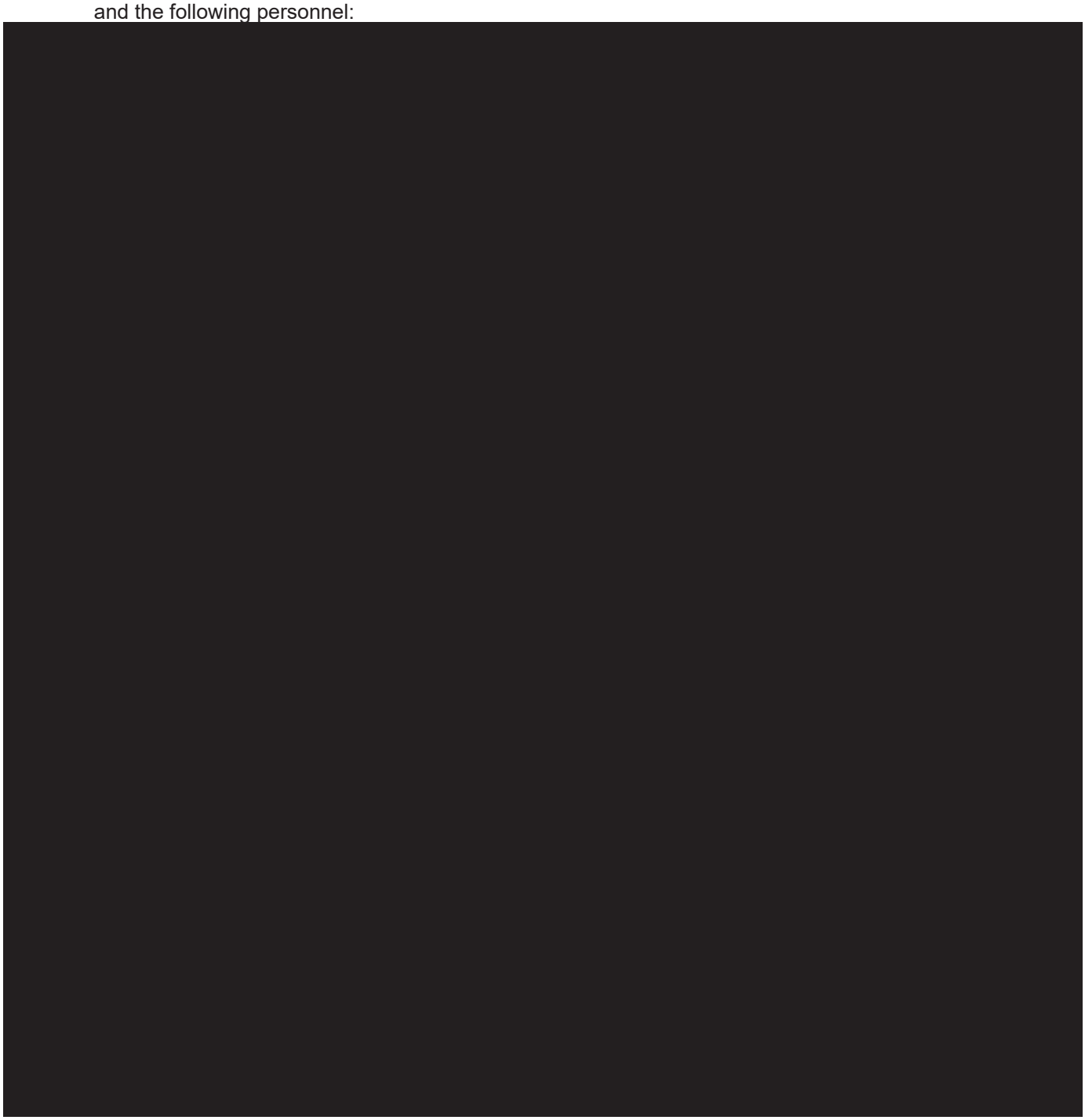
2. TABLE OF CONTENTS

3. APPROVALS

This Statistical Analysis Plan was subject to critical review and has been approved by the Sponsor and the following personnel:



4. DOCUMENT VERSION HISTORY

Document Version Number	Summary of Changes	Author Name	Document Version Date
1.0	Initial Release	[redacted]	22APR2025

5. DEFINITIONS AND ABBREVIATIONS

Term/Acronym	Definition
AD	Analysis Dataset
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BID	*Bis in die* (Twice Daily)
CI	Confidence Interval
CS	Clinically Significant
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDS-VAS	Eye Dryness Score on a Visual Analog Scale
ET	Early Termination
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
IC	Impression Cytology
ICH	International Conference on Harmonisation
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
NCS	Not Clinically Significant
NEI	National Eye Institute
OD	Right Eye
OS	Left Eye
OU	Both Eyes

Term/Acronym	Definition
[redacted]	[redacted]
PDF	Portable Document Format
PPS	Per Protocol Set
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Treatment-Emergent Serious Adverse Event
WHODrug	World Health Organization Drug Dictionary

6. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe in detail the planned analyses and reporting for protocol DEF512-E003, Amendment 2, Version 3.0 dated 21AUG2024. 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[1] entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline[2] entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

7. STUDY OBJECTIVES

7.1 Primary Study Objectives

The primary study objective is to evaluate the effect of AR-15512 ophthalmic solution 0.003% (hereafter 0.003% AR-15512) on ocular surface characteristics of subjects with dry eye disease (DED).

8. STUDY ENDPOINTS

8.1 Primary Endpoints

The primary endpoint is the percentage change from baseline in goblet cell density at Day 90 for 0.003% AR-15512.

[redacted]

8.3 Safety Endpoints

The safety endpoints include the following:

- Corrected Visual Acuity
- Slit-lamp biomicroscopy
- Adverse Events (AEs)

8.4 Statistical Hypotheses

Percentage change from baseline in goblet cell density will be tested according to the following hypothesis:

$$H_0: \mu_1 = 0$$

$$H_1: \mu_1 > 0$$

where μ_1 represents the mean percent change from baseline in goblet cell density for the 0.003% AR-15512 treatment group. This approach assesses within-group changes for 0.003% AR-15512.

9. STUDY DESIGN AND PROCEDURES

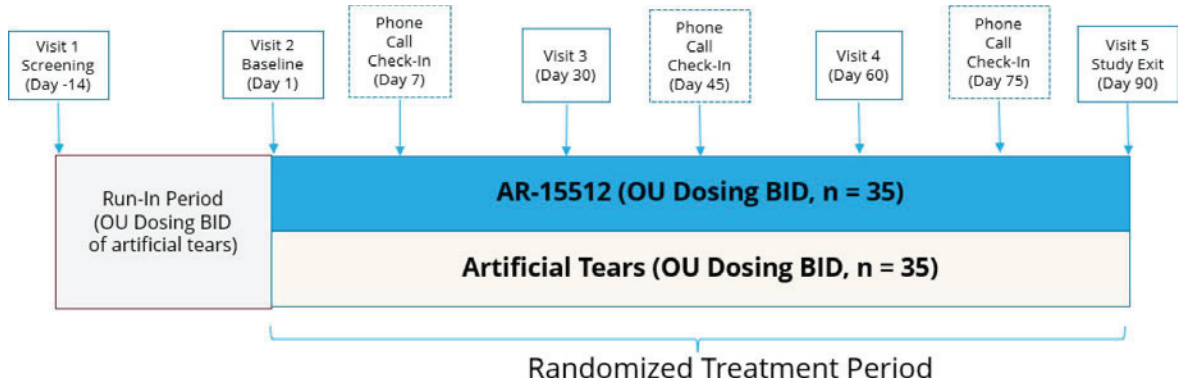
9.1 General Study Design

This is a Phase 3b, multi-center, comparator-controlled, double-masked, randomized, parallel group study conducted at approximately 4 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 Days 30, 60 and 90 (Study Exit). Telephone calls to confirm study treatment dosing compliance will be conducted on Day 7, 45 and 75.

At the end of the Screening visit, all qualified subjects will be assigned to administer Artificial Tears (REFRESH® Classic), twice daily (BID) as one drop in both eyes (OU) for approximately 14 days during the run-in period. After the run-in period, subjects will be re-evaluated at the Baseline visit for signs and symptoms of DED. Only subjects who requalify, based on inclusion/exclusion criteria, will be enrolled in the study and randomized in a 1:1 ratio within each site to receive 0.003% AR-15512 or Artificial Tears (REFRESH® Classic), to be administered as 1 drop BID OU for 90 days.

Impression cytology (IC) of the study eye will be performed at Baseline (Day 1) and on Day 90, and IC of the non-study eye will be performed on Day 30. Safety assessments will be conducted at each study visit. An overview of the study design is provided in **Figure 1**.

Figure 1. Study Design Diagram



Study visits will be referred in all tables and listings as the scheduled visit name (Screening, Day 1, Days 30, 60, and 90/Study Exit) to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Days 7, 45 and 60 were phone calls only for compliance checks and not study visits. Day 1 is the day of randomization, on which the subjects receive their first randomized 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 Randomized Study Intervention) + 1. For an event before Day 1, actual study day will be calculated as, (Date of Event) – (Date of First Dose of Randomized Study Intervention).

9.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in **Table 1**.

Table 1. Schedule of Visits and Measurements

	Start of 2 Week Run-In (Refresh Complete)	Intervention Period (BID OU, 1:1 0.003% AR-15512: Refresh Complete)							
Visit	Visit 1 Screening	Visit 2 Baseline	Phone Call	Visit 3	Phone Call	Visit 4	Phone Call	Visit 5 Study Exit	Early Termination
Visit Window (Days)	Day -14 (±3)	Day 1	Day 7 (±3)	Day 30 (±3)	Day 45 (±3)	Day 60 (±3)	Day 75 (±3)	Day 90 (±3)	
Informed consent	X								
Inclusion and exclusion criteria	X	X							
Demographics	X								
Collection of unused study treatment		X		X		X		X	X
Medical, ophthalmic, and surgical history	X								
Prior or concomitant medication review	X	X		X		X		X	X
Adverse events review	X	X	X	X	X	X	X	X	X
Urine pregnancy test (WOCBP only)	X	X						X	X
Eye dryness (EDS-VAS) questionnaire	X	X							
Corrected visual acuity	X	X		X		X		X	X
Slit-lamp biomicroscopy	X	X		X		X		X	X

Table 1. Schedule of Visits and Measurements (cont.)

	Start of 2 Week Run-In (Refresh Complete)	Intervention Period (BID OU, 1:1 0.003% AR-15512: Refresh Complete)							
Visit	**Visit 1 Screening**	**Visit 2 Baseline**	**Phone Call**	**Visit 3**	**Phone Call**	**Visit 4**	**Phone Call**	**Visit 5 Study Exit**	**Early Termination**
Visit Window (Days)	**Day -14 (+3[2])**	**Day 1**	**Day 7 (±3)**	**Day 30 (±3)**	**Day 45 (±3)**	**Day 60 (±3)**	**Day 75 (±3)**	**Day 90 (±3)**	
Fluorescein staining of cornea (modified NEI grading scale)	X	X							
Lissamine green staining of conjunctiva (modified NEI grading scale)	X	X							
At least 10 minute rest period	X								
At least a 60 minute rest period		X							
Anesthetized Schirmer test	X								
Review of qualification	X	X							
Randomization		X							
Dispensing of study treatment	X	X		X		X			
Compliance Check			X		X		X		
Impression cytology of **study eye only with EyePrim**		X						X	
In office administration of study treatment to both eyes 15-20 mins after Impression cytology on Day 1		X							
In Office administration of study treatment to both eyes on Day 30				X					

Table 1. Schedule of Visits and Measurements (cont.)

	Start of 2 Week Run-In (Refresh Complete)	Intervention Period (BID OU, 1:1 0.003% AR-15512: Refresh Complete)							
Visit	Visit 1 Screening	Visit 2 Baseline	Phone Call	Visit 3	Phone Call	Visit 4	Phone Call	Visit 5 Study Exit	Early Termination
Visit Window (Days)	Day -14 (+3[2])	Day 1	Day 7 (±3)	Day 30 (±3)	Day 45 (±3)	Day 60 (±3)	Day 75 (±3)	Day 90 (±3)	
only[1]									
3 minutes after administration of study treatment administer anesthetic to BOTH eyes (Day 30 day only)[1]				X					
[redacted]									
In office administration of study treatment to both eyes on Day 60						X			
Corrected visual acuity post impression cytology		X		X				X	
Slit-lamp biomicroscopy post impression cytology		X		X				X	
Study exit								X	X

[1] Impression cytology of the non-study eye on Day 30 can be cancelled at the Investigator's discretion, if, in their opinion, IC may negatively impact tolerability of the study medication.
Note: Subjects should be instructed to NOT take their study treatment the morning of the Clinic Visit as will be dosed in clinic (Days 30 and 60) or exited (Day 90).
[2] The Baseline Visit should be scheduled between 11 and 14 days after the Screening Visit.

9.3 Study Treatments

Study treatment for run-in period is artificial tears (REFRESH® Classic). Subjects who qualify at the Screening visit will self-administer their first dose of run-in intervention under site staff supervision. Subjects will be instructed on proper administration procedures as follows: 1 drop in each eye in the morning (from approximately 7:00h to 10:00h) and 1 drop in each eye in the evening (from approximately 19:00h to 22:00h). A new vial should be used for each administration time (both eyes dosed from one vial).

Randomized treatments assigned at Baseline visit are 0.003% AR-15512 and artificial tears (REFRESH® Classic). Following the run-in period, those subjects who requalify at the Baseline visit, will be re-instructed on proper administration procedures at the Baseline visit and the first dose of randomized treatment will be self-administered under site-staff supervision. Subjects will be instructed to administer their randomized study intervention as follows: 1 drop in each eye in the morning (from approximately 7:00h to 10:00h) and 1 drop in each eye in the evening (from approximately 19:00h to 22:00h). A new vial should be used for each administration time (both eyes dosed from one vial). The “morning” dose of randomized study intervention should not be taken prior to each follow up clinic visit (Days 30, 60 and 90) as it will be administered in-office by site staff during visits Day 30 and Day 60.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened for eligibility up to one time if there is a reasonable possibility, in the Investigator’s opinion, that the subject might meet the eligibility criteria. It is encouraged for the investigator to discuss potential rescreening with the Sponsor. The rescreened subject will be assigned a new subject ID, and the previous subject ID will be recorded in the Informed Consent electronic case report form (eCRF).

In this study, the subject ID will be in the format of xxxx-xxxx, with the first 4 characters being the site number and the last 4 characters sequentially numbered starting from 3001 within the site, which will be used to identify subjects in all datasets and listings.

10. SAMPLE SIZE

A total sample size of approximately 70 subjects will be randomized in a 1:1 ratio. With an assumption of 15% dropout rate by Day 90, this sample size (i.e., approximately 58 subjects completing Day 90) will provide at least 90% power to demonstrate the superiority of 0.003% AR-15512 over REFRESH® Classic in terms of the percent change in goblet cell density at the 5% (one-sided) significance level. The sample size calculation assumes a true effect is at least 200% in favor of 0.003% AR-15512 with standard deviations (SDs) not exceeding 350% and 75% for 0.003% AR-15512 and REFRESH®, respectively. These assumptions are based on published data regarding the effect of Cyclosporine on goblet cell density in dry eye subjects.

No data currently exists characterizing the ability of 0.003% AR-15512 to increase goblet cell density. Leveraging the literature, while plentiful, is difficult due to several important variables including method of sample collection (IC vs biopsy), conjunctival sampling location (goblet cell density is known to be distributed differently around the conjunctiva), the counting methodologies and scales

used, and the actual expression of data (absolute numbers vs percentage change vs categorical scales). However, there is precedent in the literature to support two key points: (1) a correlation exists between improvements in conjunctival staining and increases in goblet cell density and (2) sample size of 10-30 subjects per arm provide adequate power to detect treatment differences of at least a 100% change.

[redacted]

11. DATA PREPARATION

11.1 Input Data

All study data will be recorded only on the eCRFs supplied by Ora using electronic data capture (EDC) system, iMedNet.

When all prerequisites for database lock have been met, 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 Ora.

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 Ora and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.

11.2 Output Data

Data from EDC will be transferred to Ora Biostatistics and then mapped to analysis datasets (ADs). Raw data will be used to create subject listings along with ADs as needed, while all tables will be based on the ADs.

12. ANALYSIS SETS

12.1 Full Analysis Set (FAS)

The FAS includes all subjects who were randomized and received at least one dose of the study intervention. The efficacy analysis will be conducted using the FAS. The subjects will be analyzed as randomized.

12.2 Per Protocol Set (PPS)

The PPS will include all subjects in FAS having no major protocol deviation that influences efficacy. Protocol deviations will be assessed, and decisions regarding subject evaluability in the PPS will be made prior to database lock and unmasking. Subjects will be analyzed as treated. The primary efficacy analysis will be conducted using the PPS if FAS is different from PPS.

12.3 Safety Analysis Set

The Safety Analysis Set will include all subjects who have received at least one dose of study intervention. The subjects will be analyzed as treated. The safety analysis will be conducted using the Safety Analysis Set.

13. GENERAL STATISTICAL CONSIDERATIONS

13.1 Unit of Analysis

The unit of analysis will be the study eye for efficacy summaries. The study eye is defined as the eye with greatest total conjunctival lissamine green staining at Baseline. If both eyes have the same level of total conjunctival lissamine green staining, then, study eye will be the one that has the greatest total ocular staining. In the event both eyes record the same level of staining, right eye will be chosen as the study eye. The study eye will be recorded in Study Eye Determination eCRF. Non-study eye efficacy summaries will also be presented as appropriate. Safety endpoints will be presented for both study eye and non-study eye. Additionally, non-ocular AEs and medical history will be presented at the subject level.

13.2 Missing or Inconclusive Data Handling

13.2.1 Missing Dates

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 randomized study intervention and the end date is missing, or on/after the first dose of randomized study intervention, in which case missing day will be imputed as the first dose day of randomized study intervention.
- Dates with both day and month missing will be imputed as 01 Jan unless the year is same as the year of first dose of randomized study intervention and the end date is missing, or on/after the first dose of randomized study intervention, in which case missing day and month will be imputed as the first dose day and month of randomized study intervention.
- Completely missing dates will be imputed as the first dose date of randomized study intervention unless the end date is on or before the first dose date of randomized study intervention, in which case missing date will be imputed as 01 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 randomized study

intervention and the start date is on or before the last dose of randomized study intervention, in which case missing day will be imputed as the last dose day of randomized 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 randomized study intervention and the start date is on or before the last dose of randomized study intervention, in which case missing day and month will be imputed as the last dose day and month of randomized study intervention.
- If the end date is completely missing and the ongoing flag is checked, then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is not checked while the end date is missing, then the missing end date will be imputed as the later of either the start or the last dose date. For concomitant medications, if the end date is missing and the ongoing flag is checked, then the medication is considered concomitant to the treatment.

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.).

13.3 Definition of Baseline

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

- Baseline for efficacy endpoints based on EyePrim IC is the measurement at Day 1 for a given eye. When the measurement at Day 1 is missing, baseline will be missing.
- Baseline for safety assessments (corrected visual acuity and slit-lamp biomicroscopy) is the pre-IC measurements at Day 1. When pre-IC measurements at Day 1 is missing, the last non-missing measurement from Screening or any unscheduled visit prior to the initiation of randomized study intervention will be considered.

13.4 Data Analysis Conventions

All data analyses described in this SAP 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, 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 comparison will be calculated as, 0.003% AR-15512 Result - Artificial Tears Result.

All statistical tests of difference between the groups will be tested one-sided with a significance level of 0.05, with confidence intervals (CI) displayed two-sided at 90% confidence, unless otherwise

specified. Comparisons of percentages of subjects meeting a specified criteria will be tested using a Chi-square test two-sided with a significance level of 0.05. 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 based on all randomized subjects unless otherwise specified. Early termination visit (ET) and unscheduled visits will not be summarized in table summaries by visit and will only be presented in listings.

[redacted]

14. DISPOSITION OF SUBJECTS

Subject disposition will be presented in terms of the numbers of subjects who were screened, screen failed with subcategories of received run-in instillation and did not receive run-in instillation, and randomized with a subcategory of treated with the randomized study intervention. Numbers and percentages will be presented for subjects who were included in the FAS, PPS, and Safety Analysis Set; and who completed the study and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and overall for all subjects. Percentages will be calculated using randomized subjects as the denominator unless otherwise specified.

The reasons for premature study discontinuation will be summarized by treatment group and overall for all randomized subjects. The reasons for study discontinuation that will be summarized include

AE, lost to follow up, physician decision, protocol violation, site terminated by sponsor, study terminated by sponsor, withdrawal by subject, and other.

The number and percentage of subjects with any protocol deviation, major deviation, and minor deviation will be summarized by treatment group and overall for all randomized subjects.

A subject listing will be provided for subject disposition for all subjects. In addition, subject listings will be provided for informed consent, inclusion and exclusion criteria, protocol deviations, and analysis sets. Details of the study randomization, including randomization date and time, randomized treatment, and actual treatment, will also be included within a subject listing.

15. DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

15.1 Demographic Variables

The demographic variables collected in this study include age, biological sex, race, ethnicity, and iris color for each eye. Subjects who record more than one race will be grouped into a single category denoted as Multi-racial in the summary table and will be reported as collected in the subject listing. Iris color will be summarized for both study eye and non-study eye. Demographic variables will be summarized for the FAS and Safety Analysis Set, separately.

Age (years) as collected will be summarized for all subjects using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years. The number and percentage of subjects will be presented by treatment group and for all subjects, for age category, biological sex, race, ethnicity, and iris color.

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

15.2 Baseline Disease Characteristics

Baseline disease characteristics including Day 1 eye dryness score on a visual analog scale (EDS-VAS), study eye and non-study eye results for Day 1 total corneal fluorescein staining score (modified National Eye Institute [NEI] scale), total conjunctival lissamine green staining score (modified NEI scale), 6 individual zone lissamine green staining score (for study eye only), total staining ocular score (sum of corneal and conjunctival staining, modified NEI scale), as well as anesthetized Schirmer score at Screening will be summarized using continuous descriptive statistics for FAS. EDS-VAS questionnaire, sodium fluorescein staining of cornea (modified NEI grading scale), lissamine green staining of conjunctiva (modified NEI grading scale), and anesthetized Schirmer test are pre-treatment assessments collected only before randomization. Details of pre-treatment assessments are described in Section 15.2.1, Section 15.2.2, Section 15.2.3, and Section 15.2.4. Subject listings will be provided for EDS-VAS, fluorescein staining of cornea, lissamine green staining of conjunctiva, and anesthetized Schirmer test separately.

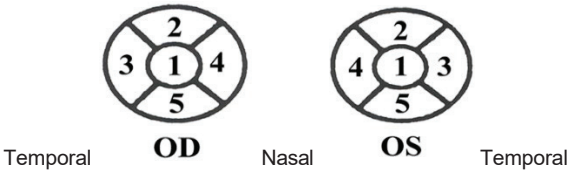
15.2.1 EDS - VAS QUESTIONNAIRE

The EDS-VAS questionnaire will be performed at Screening and Day 1 before randomization. Subjects will be asked to rate the severity of their eye dryness (both eyes together) over the last 24 hours on a VAS by placing a vertical mark on the 100-mm horizontal line to indicate the severity of their eye dryness, with 0 corresponding to “no eye dryness” and 100 corresponding to “maximum eye dryness.”

15.2.2 Sodium Fluorescein Staining of Cornea (Modified NEI Grading Scale)

Sodium fluorescein staining of cornea (modified NEI grading scale) for both eyes will be performed at Screening and Day 1 before randomization. The grading of the resulting corneal staining will be based on the modified NEI workshop grading scheme (**Figure 2**). Each of the 5 zones (zone 1: central; zone 2: superior; zone 3: temporal; zone 4: nasal; zone 5: inferior) on the cornea of each eye are to be graded (0-4 for each zone). Half (0.5) grade increments may be used. The total corneal staining score for each eye will be collected in eCRF, which is calculated as the sum of the grading score of 5 zones. The maximum possible score for the total corneal staining score per eye is 20. Higher total scores indicate greater staining (or worse conditions).

Figure 2. Modified NEI Corneal Staining Grading Scheme



Grade each zone using the dot count scale:

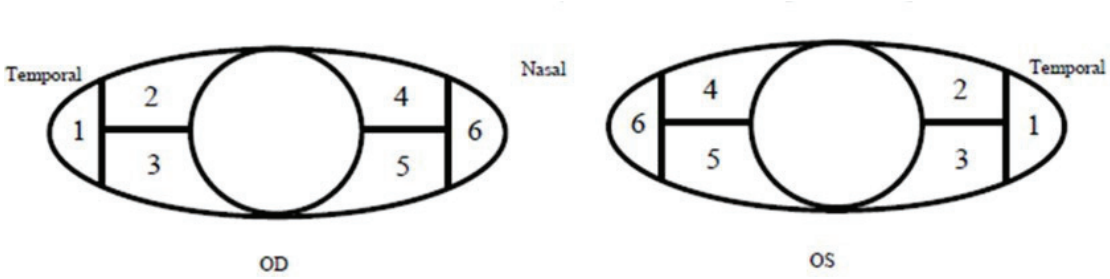
Score	Description
0	No punctate stain in the area
0.5	1–5 micropunctate stain spots
1.0	6–15 micropunctate stain spots
1.5	More than 15 micropunctate stain spots
2.0	Moderate macropunctate stain spots (involving <50% of the area)
2.5	Moderate macropunctate stain spots (involving >50% of the area)
3.0	Clumped macropunctate stain spots (involving <50% of the area)
3.5	Clumped macropunctate stain spots (involving >50% of the area)
4.0	Severe diffuse (coalescent) macropunctate stain of the area

15.2.3 Lissamine Green Staining of the Conjunctiva Based on the Modified National Eye Institute Grading Scheme

Lissamine green staining of conjunctiva (modified NEI grading scale) for both eyes will be performed at Screening and Day 1 before randomization. The 6 conjunctival zones (zones 1, 2, and 3 are temporal and zones 4, 5 and 6 are nasal) will be graded using the modified NEI grading scheme (score between 0 and 4 per zone). The schematic representation of the 6 conjunctival zones per eye is shown in **Figure 3**. Half (0.5) grade increments may be used. The total conjunctival staining score

for each eye will be collected in eCRF, which is calculated as the sum of grading score of 6 zones. The maximum possible score for total conjunctival staining score per eye is 24. Higher scores indicate greater staining (or worse condition).

Figure 3. Modified NEI Conjunctival Staining Grading Scheme



Grade each zone using the dot count scale:

Score	Description
0	No punctate stain in the area
0.5	1–5 micropunctate stain spots
1.0	6–15 micropunctate stain spots
1.5	More than 15 micropunctate stain spots
2.0	Moderate macropunctate stain spots (involving <50% of the area)
2.5	Moderate macropunctate stain spots (involving >50% of the area)
3.0	Clumped macropunctate stain spots (involving <50% of the area)
3.5	Clumped macropunctate stain spots (involving >50% of the area)
4.0	Severe diffuse (coalescent) macropunctate stain of the area

15.2.4 Anesthetized Schirmer Test

The anesthetized Schirmer test for both eyes will be performed only at the Screening visit. The test score will be collected in the unit of millimeters (mm). Higher scores indicate better condition.

16. MEDICAL HISTORY AND CONCOMITANT MEDICATIONS

Subject listings of medical history, prior and concomitant medications, and concomitant procedures will be generated.

16.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 27.1 and presented with System Organ Class (SOC) and Preferred Term (PT). Medical history will be summarized using Safety Analysis Set using discrete summary statistics for all subjects at the subject level 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. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs are ordered in

ascending alphabetical order, and PTs within an SOC are sorted by descending frequency for all subjects.

16.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug; Global, B3, September 2024) 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.

Prior medications are defined as those medications that ended prior to the administration of the randomized study intervention. Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of randomized study intervention administration and continuing for any period of time following the administration of randomized study intervention or (2) at any time following the administration of randomized study intervention. Prior medications will be identified in the listing.

Concomitant medications will be summarized using the Safety Analysis Set. Medications will be tabulated for all subjects using frequencies and percentages. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. In the summaries, ATC Classes and preferred names within ATC Class will be presented in ascending alphabetical order.

16.3 Concomitant Procedures

Concomitant procedures will be coded using MedDRA Version 27.1 and will be presented in a listing with SOCs and PTs.

17. DOSING COMPLIANCE AND TREATMENT EXPOSURE

In addition to the analyses described in the following sections, subject listings will be provided for in-office randomized study intervention instillation, run-in intervention and randomized study intervention dispensation, run-in intervention and randomized study intervention accountability, and phone calls for checking subjects' compliance. Dosing compliance for run-in kit will be calculated by sites to record in eCRF, which will be presented in the accountability listing.

17.1 Dosing Compliance

The overall dosing compliance in percentage for the randomized study intervention over the course of the study (starting from Day 1 till study exit) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

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

The number of actual doses received will be calculated as the sum of the number of used vials recorded in the Study Drug Accountability eCRF, with subject(s) excluded from the compliance calculation if the eCRF does not contain drug return details. The number of expected doses will be calculated as:

Number of Expected Doses = 2 x [(Date of Last Dose - Date of First Dose) + 1]

for all subjects, regardless of study completion status. The date of last dose will be recorded in the End of Study eCRF, when missing, it will be the latest non-missing dosing date recorded in the Instillation eCRF. The date of first dose will be the earliest randomized study intervention dosing date in the Instillation eCRF.

A categorical dosing compliance variable will also be derived as non-compliant (< 70%), compliant (≥ 70% and ≤ 130%), and over compliant (> 130%).

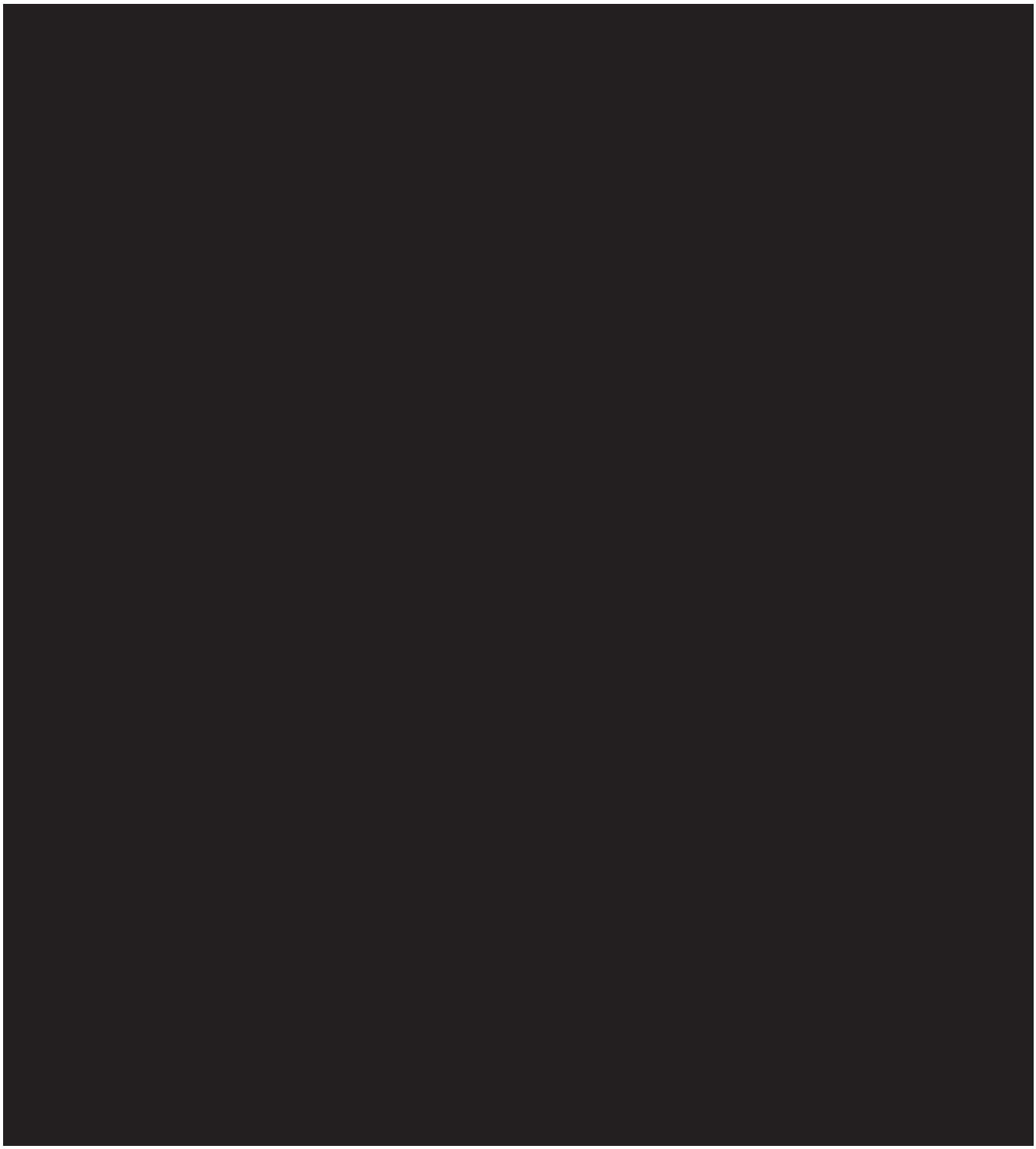
Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group using the Safety Analysis Set. The compliance category defined above will be summarized with discrete summary statistics. The calculated overall dosing compliance result for each subject will be presented in the accountability listing.

17.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

Extent of Exposure (days) = (Date of Last Dose - Date of First Dose) + 1

Extent of treatment exposure for each subject exposed to randomized study intervention will be summarized with continuous descriptive statistics for each treatment group using the Safety Analysis Set. In addition, the number of subjects with treatment exposure ≥87 days and <87 days will be summarized using counts and percentages.



18.2 Primary Analysis of Primary Efficacy Variables

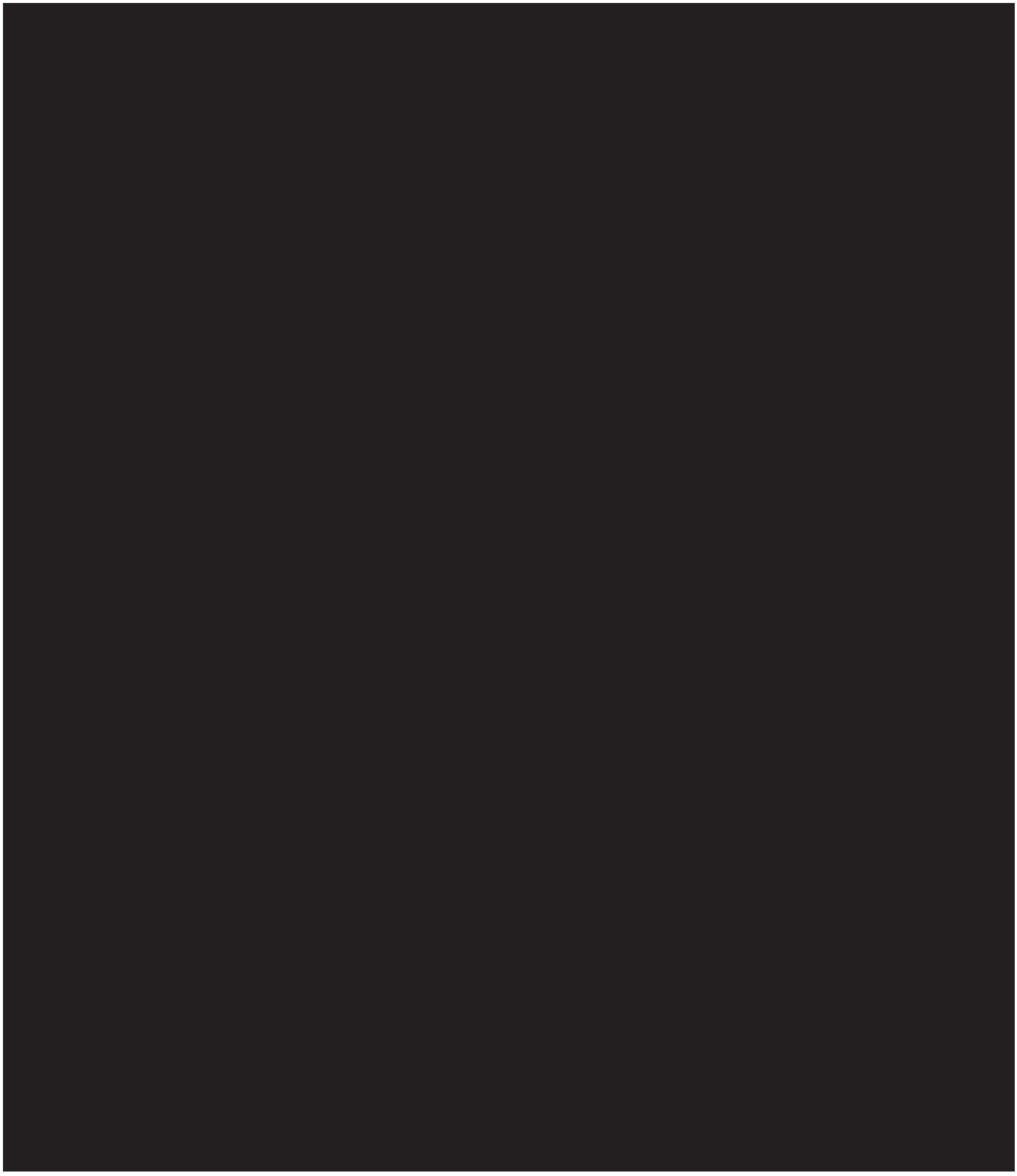
The primary endpoint will focus on the percentage change from baseline in goblet cell density at Day 90 for 0.003% AR-15512. The analysis will be performed based on the raw values in the unit of cells/mm^2 using FAS and PPS when PPS is different from FAS. Mean goblet cell density rounded to the same precision as the collected individual values will be calculated based on the non-missing results from the 5 fields of each analyzed IC sample at a given visit, which will be used as the basis for the goblet cell density summary. Percentage change from baseline is calculated as the following

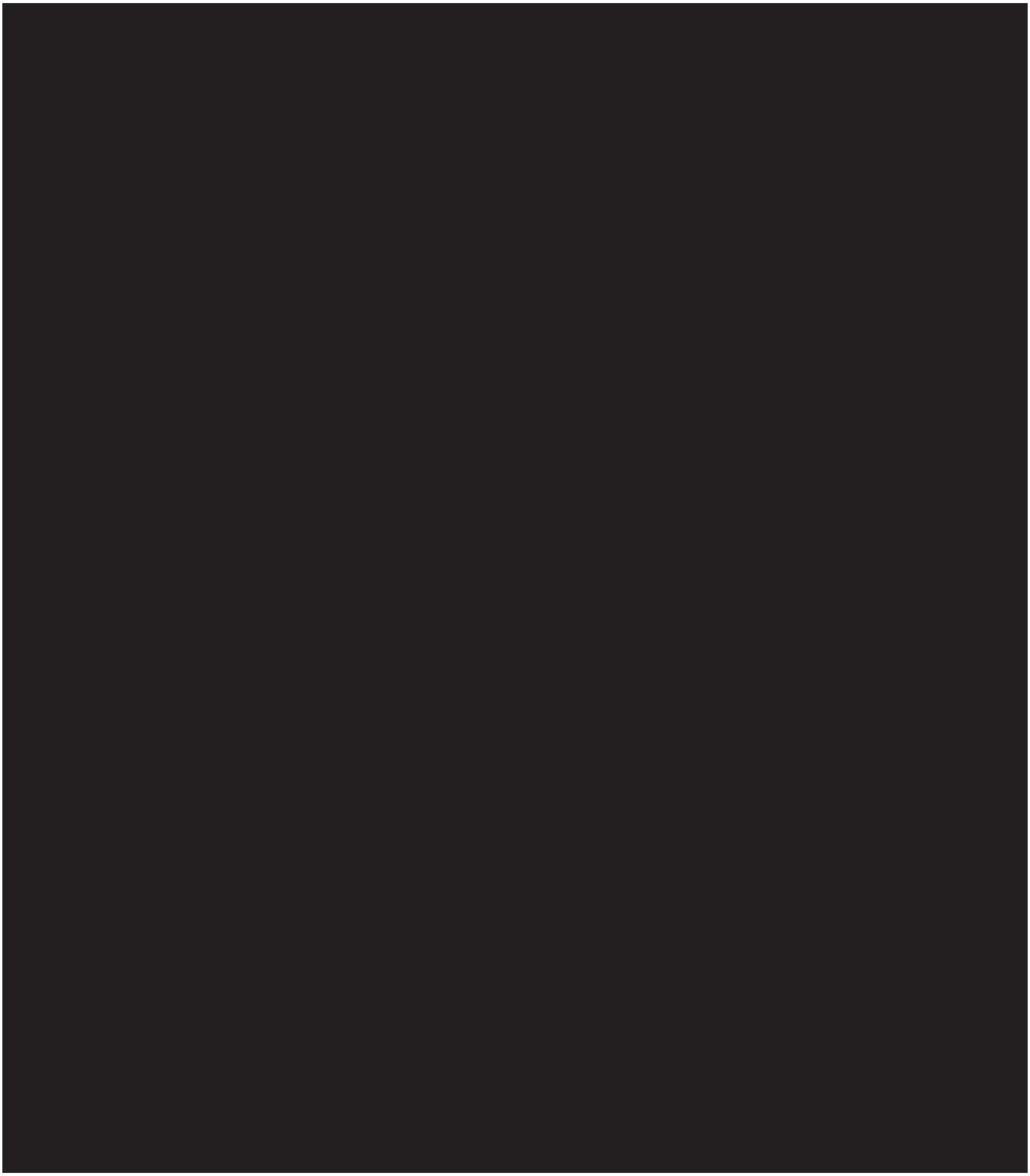
formula. The percentage will be missing when goblet cell density is missing at either baseline or Day 90 or when baseline goblet cell density is reported as zero.

$$\frac{(\text{Goblet Cell Density at Day 90-Baseline Goblet Cell Density})}{\text{Baseline Goblet Cell Density}} \times 100$$

An analysis of covariance (ANCOVA) model will be used to evaluate the percentage change from baseline in goblet cell density within each treatment group, adjusting for baseline goblet cell density as a covariate. For each treatment group, continuous descriptive statistics will be provided for percentage change from baseline in goblet cell density along with least squares (LS) means, standard error (SE), 90% CIs and p-value for LS mean from the ANCOVA model.

The primary hypothesis, as specified in Section 8.4, will assess whether the mean percentage change from baseline in goblet cell density is significantly greater than zero within the 0.003% AR-15512 treatment group. If the mean percentage change from baseline in goblet cell density in the 0.003% AR-15512 treatment group is significantly greater than zero, then the study will be deemed successful.





19. SAFETY ANALYSES

All safety analyses will be conducted using the Safety Analysis Set.

19.1 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. AEs should be documented from the time the subject provides informed consent until subject participation in the study has been completed. Any medical condition present prior to informed consent which remains unchanged or improved should not be recorded as an AE at subsequent visits. However, an AE should be recorded if the frequency, intensity, or the character of a pre-existing condition worsens during the study period beyond what would be expected from the natural progression of that condition. All AEs will be coded using the MedDRA Version 27.1.

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 or procedure, and the expectedness of each AE (unexpected and expected) should be determined by the Investigator.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the dose of randomized study intervention. Only TEAEs will be summarized, however all AEs collected in the eCRF will be presented in data listings.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one TEAE. This summary will also include

breakdowns of TEAEs further categorized as ocular (right eye [OD], left eye [OS], and OU separately) or non-ocular, TEAEs related (defined as either related or possibly related) to study intervention, treatment-emergent serious adverse events (TE-SAEs), TE-SAEs related to study intervention, TEAEs leading to study intervention discontinuation, TEAEs leading to death, TEAEs by maximum severity, and TEAEs by strongest relationship to study intervention.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE and classified by MedDRA SOC and PT. If a subject reports multiple TEAEs to the same SOC or multiple PTs within the same SOC, the subject will be counted only once within that SOC or PT. In the summaries, SOCs will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency within each SOC based on the count for 0.003% AR-15512 treatment.

Separate summaries by SOC and PT will be provided for the following categories of AEs:

- TEAEs
- Treatment-related TEAEs
- TE-SAEs

Summaries of TEAEs by maximum severity and the TEAEs by the strongest relationship to the study intervention will be presented. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT 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 an SOC, the subject will be counted once under the maximum severity or the strongest relationship.

All AEs will be presented in a subject listing.

19.2 Corrected Visual Acuity

The logarithm of the minimum angle of resolution (logMAR) visual acuity will be assessed in both eyes using an Early Treatment Diabetic Retinography Study (ETDRS) Series 2000 chart at Screening, Day 1 (pre-IC and post-IC), Day 30 (pre-IC and post-IC), Day 60, and Day 90 (pre-IC and post-IC).

The observed and change from baseline visual acuity will be summarized for each eye (study eye and non-study eye) using continuous descriptive statistics. A subject listing of corrected visual acuity will be produced.

19.3 Slit-Lamp Biomicroscopy

A slit-lamp biomicroscopy examination of the eyelid (erythema, edema), conjunctiva (hyperemia, edema), cornea (edema, staining/erosion), anterior chamber (cells, flare), iris, and lens (lens status, lens opacity for phakic only) will be performed for both eyes at Screening, Day 1 (pre-IC and post-IC), Day 30 (pre-IC and post-IC), Day 60, and Day 90 (pre-IC and post-IC). The findings will be graded for clinical significance (CS) and non-clinical significance (NCS).

Shift tables of score values will be provided comparing post-baseline visit/time point to baseline for both eyes (study eye and non-study eye) separately. A subject listing of the slit-lamp biomicroscopy parameters will be produced.

20. INTERIM ANALYSES

No interim analysis will be performed in this study.

[redacted]

22. 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.

23. PLANNED OUTPUT

23.1 Tables

No topline outputs are planned for this study.

Number	Title	Population
Table 14.1.1	Subject Disposition	All Subjects
Table 14.1.2.1.1	Demographics	Full Analysis Set
Table 14.1.2.1.2	Demographics	Safety Analysis Set
Table 14.1.2.2	Baseline Disease Characteristics	Full Analysis Set
Table 14.1.3	Medical History	Safety Analysis Set
Table 14.1.4	Concomitant Medications	Safety Analysis Set
Table 14.1.5.1	Dosing Compliance for Randomized Study Intervention	Safety Analysis Set
Table 14.1.5.2	Treatment Exposure Duration for Randomized Study Intervention	Safety Analysis Set
Table 14.2.1.1	Percent Change from Baseline in Study Eye Goblet Cell Density (cells/mm^2) at Day 90	Full Analysis Set

[redacted]

Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety Analysis Set
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.3	Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set

Number	Title	Population
Table 14.3.1.4	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.5	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Analysis Set
Table 14.3.1.6	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Strongest Relationship to Study Intervention	Safety Analysis Set
Table 14.3.2	Actual and Change from Baseline in Corrected Visual Acuity in logMAR Score by Visit	Safety Analysis Set
Table 14.3.3	Shift in Slit-Lamp Biomicroscopy Results by Visit	Safety Analysis Set

23.2 Listings

Number	Title	Population
Listing 16.1.7	Screening and Treatment Randomization	Randomized Subjects
Listing 16.2.1.1	Subject Disposition	All Subjects
Listing 16.2.1.2	Informed Consent	All Subjects
Listing 16.2.2.1	Inclusion/Exclusion Criteria	All Subjects
Listing 16.2.2.2	Protocol Deviations	Randomized Subjects
Listing 16.2.3	Analysis Sets	Randomized Subjects
Listing 16.2.4.1.1	Demographics	Randomized Subjects
Listing 16.2.4.1.2	Childbearing Potential	Randomized Female Subjects
Listing 16.2.4.2	Medical History	Randomized Subjects
Listing 16.2.4.3	Prior and Concomitant Medications	Randomized Subjects
Listing 16.2.4.4	Concomitant Procedures	Randomized Subjects
Listing 16.2.4.5	Eye Dryness (EDS-VAS)	Randomized Subjects
Listing 16.2.4.6	Fluorescein Staining of Cornea – Modified NEI Grading Scale	Randomized Subjects
Listing 16.2.4.7	Lissamine Green Staining of Conjunctiva – Modified NEI Grading Scale	Randomized Subjects
Listing 16.2.4.8	Anesthetized Schirmer Test	Randomized Subjects
Listing 16.2.5.1	In-Office Run-in Intervention and Randomized Study Intervention Instillation	Randomized Subjects

Number	Title	Population
Listing 16.2.5.2	Run-in Intervention and Randomized Study Intervention Dispensation	Randomized Subjects
Listing 16.2.5.3	Run-in Intervention and Randomized Study Intervention Accountability	Randomized Subjects
Listing 16.2.5.4	Phone Call	Randomized Subjects
Listing 16.2.6.1.1	Impression Cytology (IC) Sample Collection	Randomized Subjects
Listing 16.2.6.1.2	Impression Cytology (IC) Sample Results	Randomized Subjects
Listing 16.2.7	Adverse Events	All Subjects
Listing 16.2.8.1	Corrected Visual Acuity (CVA)	Randomized Subjects
Listing 16.2.8.2	Slit-Lamp Biomicroscopy	Randomized Subjects
Listing 16.2.9	Urine Pregnancy Test	Randomized Female Subjects
Listing 16.2.10	Unscheduled Visit	Randomized Subjects

Electronic Record and Signature Disclosure created on: 17-Nov-2021 | 11:28

Parties agreed to: Agustin Calatroni, Jenny Jones, Michelle Senchyna, Rebecca Mestek, Ryan Thompson, Yan Liu, Riya Kohli