A Phase 3b Study to Evaluate 0.003% AR-15512 Safety and Drop Attributes

STUDY ID

DEF512-E005

STATISTICAL ANALYSIS PLAN v.1

12 Mar 2025

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1. TITLE PAGE

A Phase 3b Study to Evaluate 0.003% AR-15512 Safety and Drop Attributes

Sponsor:	Alcon Research, LLC (Alcon) 6210 South Freeway Forth Worth, Texas 76134-2099 USA
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2. TABLE OF CONTENTS

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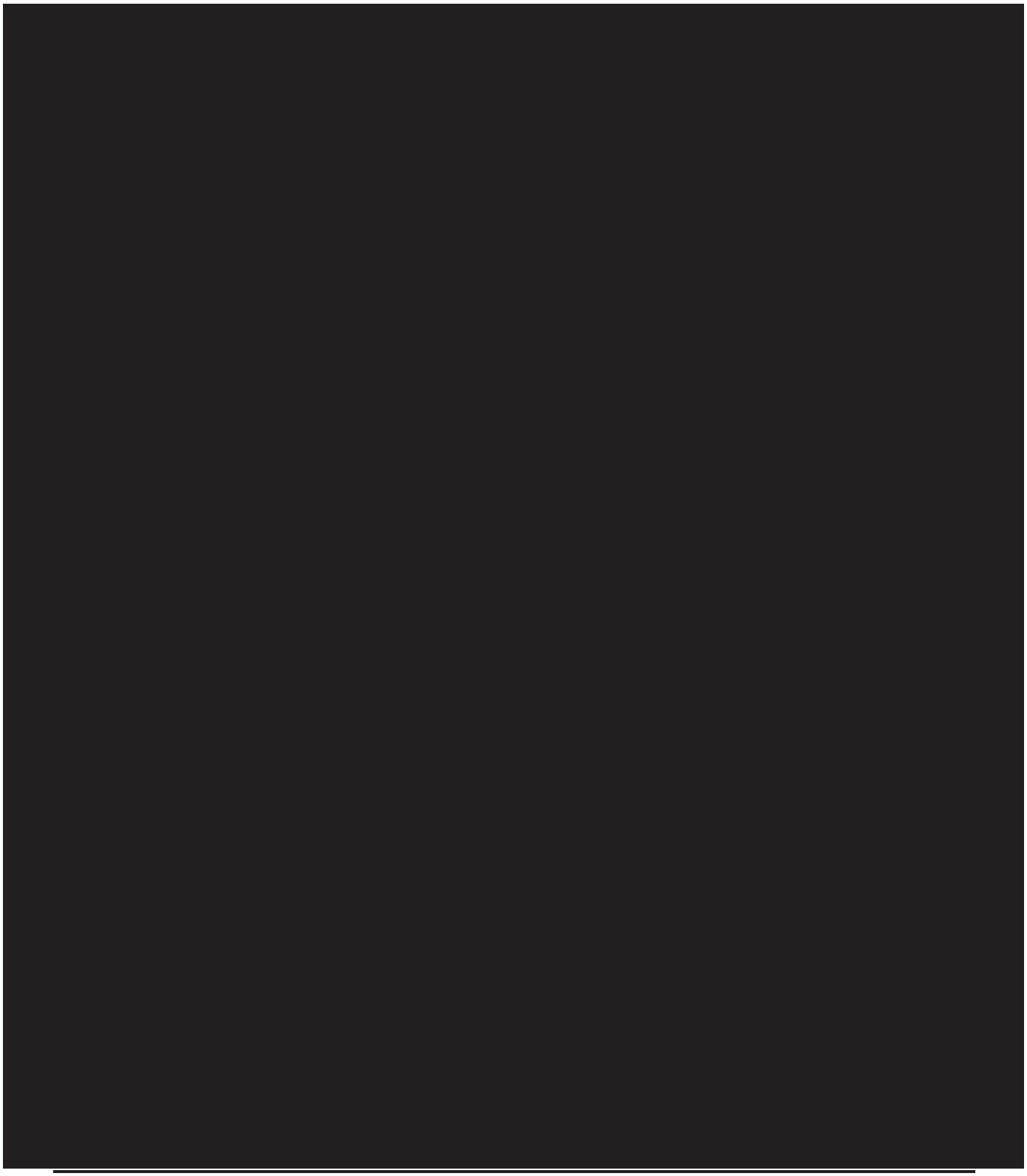

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5. DEFINITIONS AND ABBREVIATIONS

Term/Acronym	Definition
512	AR-15512 Ophthalmic Solution 0.003%
AD	Analysis Dataset
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
CI	Confidence Interval
[redacted]	[redacted]
CS	Clinically Significant
CVA	Corrected Visual Acuity
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EC	Eye Closure
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
[redacted]	[redacted]
ICH	International Conference on Harmonisation
IV	Instillation Variation
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
NCS	Not Clinically Significant
OD	Right Eye
OS	Left Eye

Term/Acronym	Definition
PDF	Portable Document Format
[redacted]	[redacted]
PT	Preferred Term
RC	Refresh Classic
RT	Room Temperature
RTF	Rich Text Format
SAE	Serious Adverse Event
SAF	Safety Analysis Set
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
WOCBP	Women of Childbearing Potential

6. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe in detail the planned analyses and reporting for protocol DEF512-E005, Amendment 1, Version 2.0 dated 08JAN2025. 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 objectives are to evaluate the proportion of ocular adverse events (AEs) reported in subjects with dry eye disease (DED) between the intervention arm 0.003% AR-15512 (512) vs Refresh® Classic (artificial tears).

[redacted]

8. STUDY ENDPOINTS

8.1 Primary Endpoints

The primary endpoint is proportion of ocular AEs reported by intervention arm (512 vs Refresh Classic).

[redacted]

[redacted]

8.3 Safety Endpoints

The safety endpoints include the following:

- Corrected Visual Acuity (CVA)
- Slit-Lamp Biomicroscopy
- AEs

[redacted]

9. STUDY DESIGN AND PROCEDURES

9.1 General Study Design

This is a Phase 3b, subject-masked, randomized, single-visit, crossover design conducted in the United States at approximately 6 sites.

Approximately 36 to 55 DED subjects will be enrolled. The study will consist of 1 Visit (Screening, Enrollment, Assessments). All subjects will be exited from the study at the end of the Study Visit.

At the end of the Screening phase, all qualified subjects will be enrolled and instilled a drop of Refresh Classic in the **right eye only**. All subjects will then be dosed with 512 under four different instillation variations as described in Table 1. Subjects will be randomized to one of the four sequences of 512 instillation variations based on a Williams design randomization sequence (Table 2).

Each 512 instillation variation will be dosed in one **(1) eye only** as described in the randomization sequence (Table 2), starting with the **left eye**. After the first two 512 instillation variations are complete, subjects will start a wait period of a minimum of 2 hours and a maximum of 3 hours prior to the completion of dosing of the remaining two 512 instillation variations. A wait period of 30 minutes ± 5 minutes will take place between left eye and right eye instillation. [redacted] An overview of the study design can be found in Figure 1.

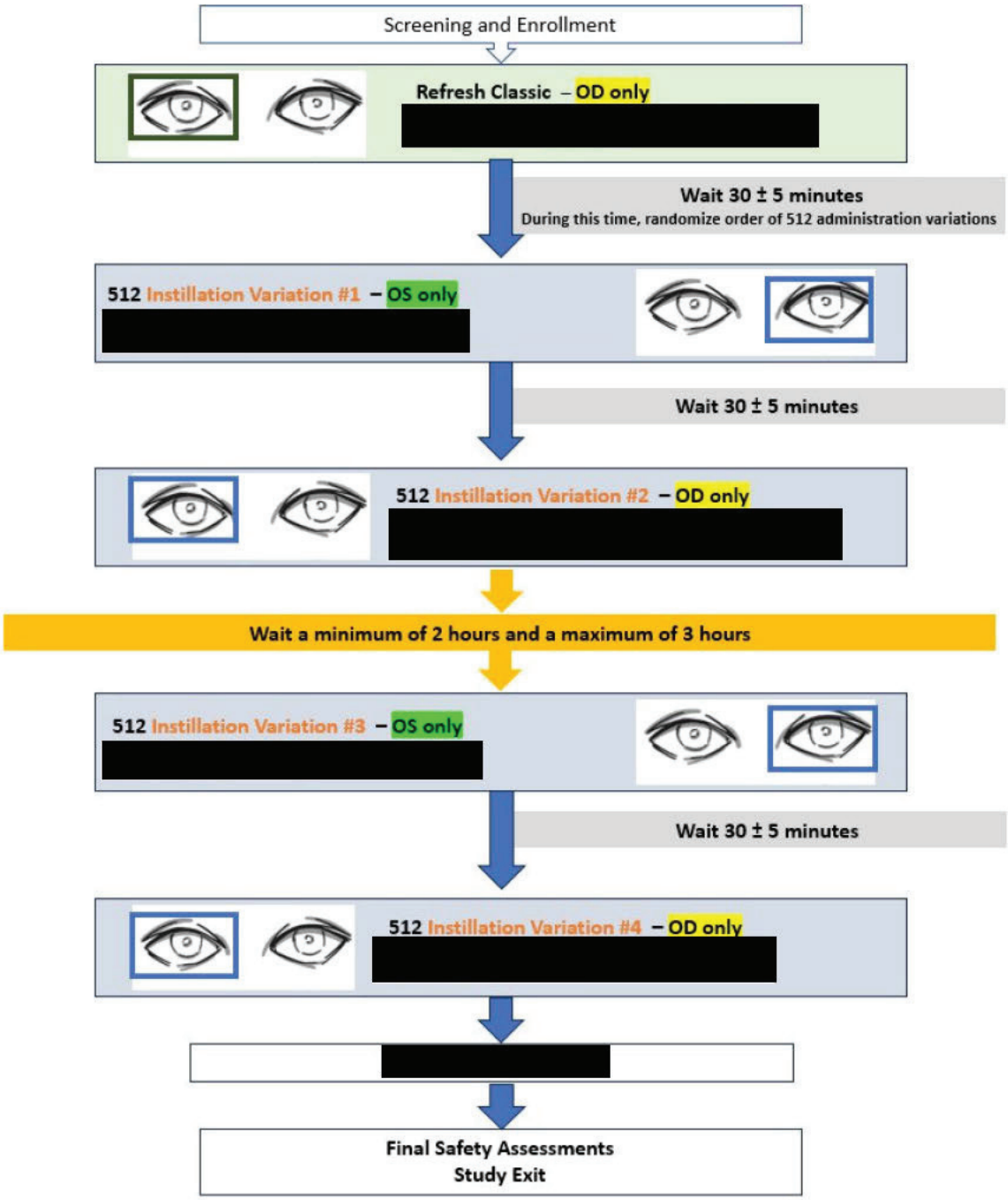
Table 1. Summary of 0.003% AR-15512 Instillation Variations

Instillation Variation Name	Instillation Variation Description
512-RT (base case)	0.003% AR-15512 instilled at room temperature, eyes to remain open post-drop instillation.
512-COLD	0.003% AR-15512 stored in refrigerator [redacted] and instilled immediately [redacted] after removal from refrigerator, eyes to remain open post-drop instillation.
512-RT-EC	0.003% AR-15512 instilled at room temperature followed by subjects immediately closing their eyes [redacted]
512-COLD-EC	0.003% AR-15512 stored in refrigerator [redacted] and instilled immediately ([redacted] post removal from refrigerator followed by subjects immediately closing their eyes [redacted]

Table 2. Randomization Sequences Using a Williams Design for 0.003% AR-15512 Instillation Variations

Sequence	Period			
	1	2	3	4
1	512-RT	512-COLD	512-RT-EC	512-COLD-EC
2	512-RT-EC	512-RT	512-COLD-EC	512-COLD
3	512-COLD	512-COLD-EC	512-RT	512-RT-EC
4	512-COLD-EC	512-RT-EC	512-COLD	512-RT

Figure 1. Study Design Diagram



Timepoints will be referred to in tables and listings as applicable to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Specifically, for safety assessments (CVA, slit-lamp), timepoints (pre-drop, post-last drop) will be used to refer to the assessment prior to any drop of study intervention instillation (Refresh Classic and 512 variations; i.e., before study enrollment) and after the last drop of 512 instillation variation. [redacted]

[redacted]

9.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in Table 3.

Table 3. Schedule of Visits and Assessments

Assessment	
Informed consent	X
Demographics	X
Medical, ophthalmic, and surgical history	X
Prior or concomitant medication review	X
Urine pregnancy test (WOCBP only)	X
Corrected visual acuity *(pre-drop)*	X
Slit lamp biomicroscopy *(pre-drop)*	X
Inclusion and exclusion criteria review	X
Study Enrollment	X
Instillation of 1 drop of Refresh Classic to right eye	X
[redacted]	
30 min ± 5 min wait	X
Randomization to order the sequence of 512 instillation variation (may occur during the 30 min ± 5 min wait period)	X
Instill **first** randomized 512 instillation variation to left eye	X
[redacted]	
30 min ± 5 min wait	X
Instill **second** randomized 512 instillation variation to right eye	X
[redacted]	
Minimum 2 hour and Maximum 3 hour wait	X
Instill **third** randomized 512 instillation variation to left eye	X
[redacted]	
30 min ± 5 min wait	X
Instill **fourth** randomized 512 instillation variation to right eye	X
[redacted]	

Assessment	
Corrected visual acuity *(post-last drop)*	X
Slit lamp biomicroscopy *(post-last drop)*	X
Adverse events	X
Study Exit	X
Abbreviations: min = minutes; WOCBP = women of childbearing potential	

9.3 Study Treatments

- AR-15512 ophthalmic solution 0.003% (post-randomization study intervention)
- Refresh Classic (pre-randomization study intervention)

10. SAMPLE SIZE

No power calculation will be used to determine the sample size. [redacted] he study aims to recruit approximately 36 to 55 subjects.

11. DATA PREPARATION

11.1 Input Data

Study data will be recorded on the electronic Case Report Forms (eCRFs) supplied by Ora using electronic data capture (EDC) system, iMedNet. In addition, the assigned categories of the Post Drop Questionnaire outside the EDC system will be obtained based on sponsor committee evaluations and sent to Ora for analysis. This data source will be described in a note-to-file to be written by Ora, reviewed and approved by Alcon, and documented in the final trial master file.

When all prerequisites for database lock have been met, the database will be locked. 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 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 POPULATIONS

12.1 Safety Analysis Set (SAF)

The SAF will include all subjects who received at least one dose of Refresh Classic or one dose of 512. The safety analyses will be performed using SAF. Subjects in the SAF will be analyzed as treated.

12.2 Full Analysis Set (FAS)

The FAS will include all randomized subjects who have received at least one dose of Refresh Classic and one dose of 512 instillation variation and who have at least one rating of the Rating Sensation Assessment. The exploratory analyses will be performed using FAS. Subjects in the FAS will be analyzed as randomized.

[redacted]

13. GENERAL STATISTICAL CONSIDERATIONS

13.1 Unit of Analysis

[redacted]. Treatment-emergent adverse events (TEAEs) will be summarized at the subject level. [redacted]

13.2 Missing or Inconclusive Data Handling

13.2.1 Missing Dates

Given this is a one-visit study, all AEs will be considered as treatment-emergent unless otherwise indicated from the data that it is not treatment-emergent. No imputation of missing or partial AE dates will be performed. All medications will be considered concomitant medications unless there are clear indications from data that the medications ended before study intervention administration. No imputation for missing or partial dates for concomitant medications will be performed.

[redacted]

[redacted]

14. DISPOSITION OF SUBJECTS

Subject disposition will be presented for all subjects in terms of the number of subjects who were screened, screen failed, enrolled (i.e., subjects who signed informed consent and were not screen failures), instilled with Refresh Classic, and randomized, with subcategories of instilled with IV1, IV2, IV3, or IV4 in a given period (Table 2). Numbers and percentages will be presented for subjects who were included in the FAS, [redacted] and SAF; and who completed the study and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. Percentages will be calculated using randomized subjects in the respective 512 randomization sequence as the denominator unless otherwise specified.

The reasons for premature study discontinuation will be summarized for all discontinued subjects with percentages calculated. The reasons for study discontinuation that will be summarized include AE, lost to follow up, physician decision, protocol violation, study terminated by sponsor, withdrawal by subject, site terminated by sponsor, and other.

The number and percentage of subjects with any deviation, major deviation, and minor deviation will be summarized by 512 randomization sequence and for all 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. A separate listing will also be provided for screening and 512 randomization sequence.

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 right eye (OD) and left eye (OS). Demographic variables will be summarized for the FAS and SAF 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 512 randomization sequence 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, a separate subject listing will be provided for the childbearing potential and pregnancy test results for female subjects in SAF.

16. MEDICAL HISTORY AND CONCOMITANT MEDICATIONS

Subject listings of medical history (ocular and non-ocular), prior and concomitant medications, and concomitant procedures will be generated, but no summaries are planned.

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).

16.2 Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug B3, September 2024) and presented with the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, 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), the drug name will be used as the preferred name.

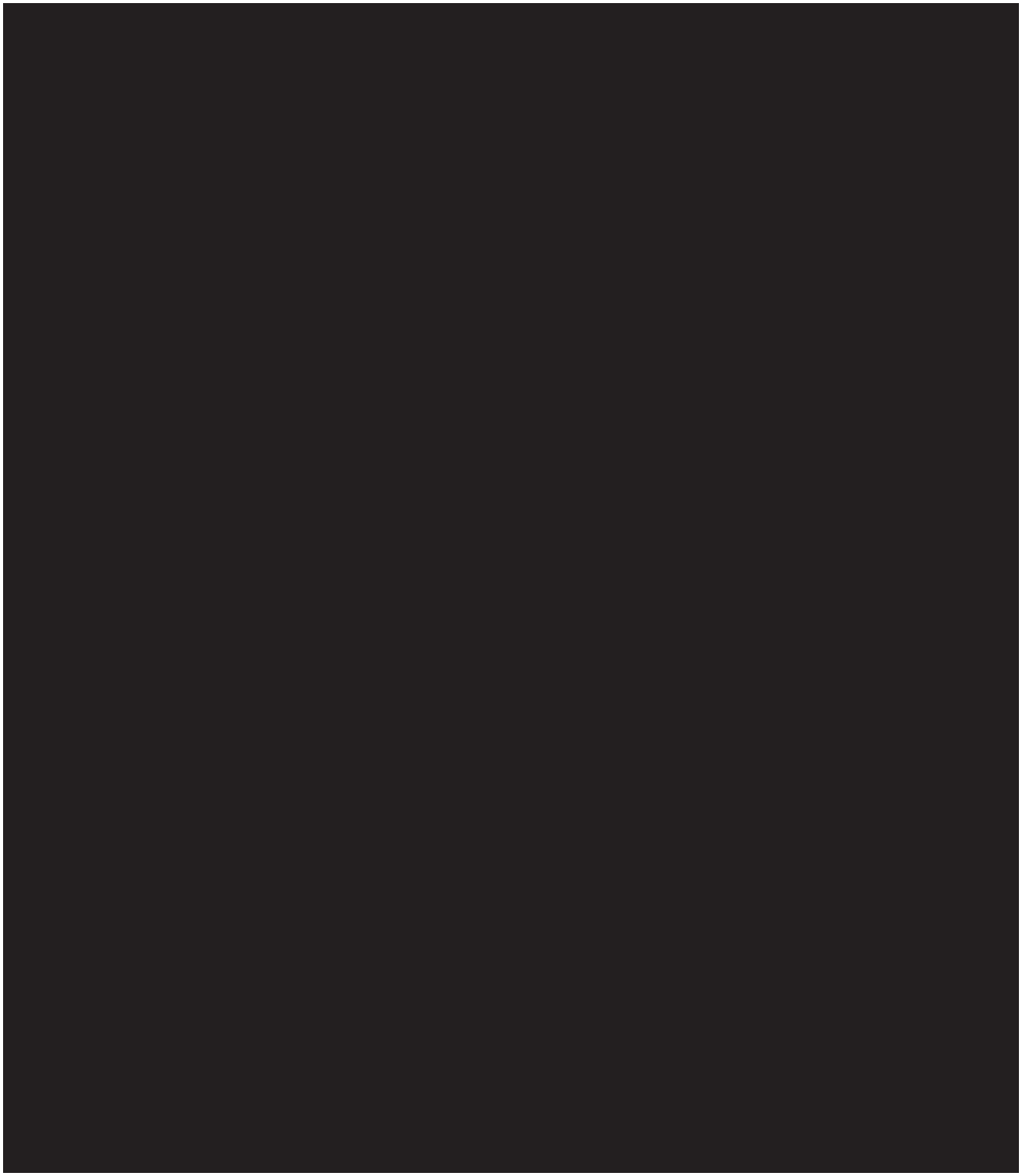
Prior medications are defined as those medications taken within 30 days and discontinued before the date of study intervention administration. Concomitant medications are defined as those medications listed as having been taken (1) prior to the date of study intervention administration and will continue for any period of time following the administration of study intervention or (2) at any time following the administration of study intervention. Prior medications will be identified in the listing.

16.3 Concomitant Procedures

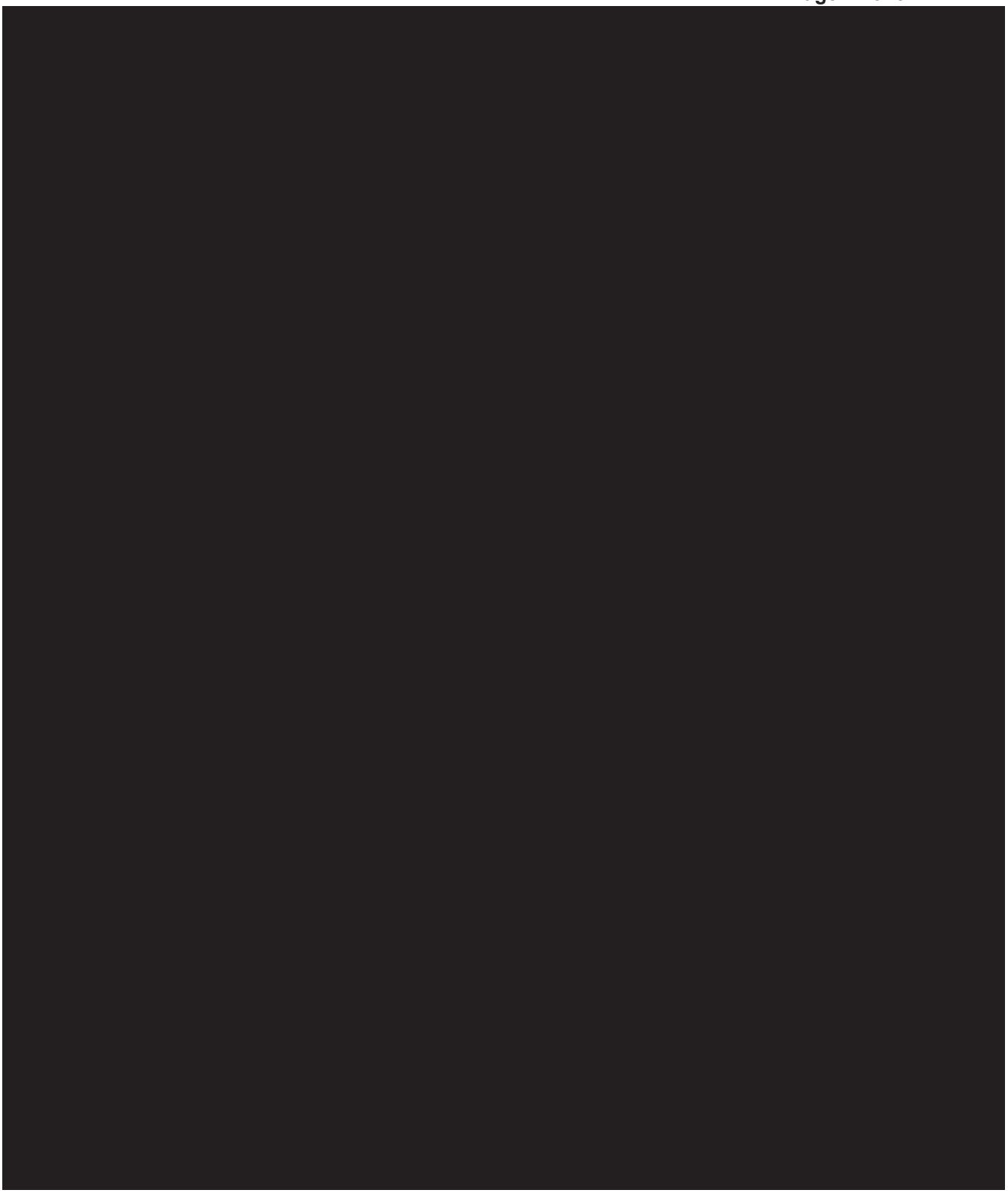
Concomitant procedures will be coded using MedDRA Version 27.1 and presented with SOC and PT.

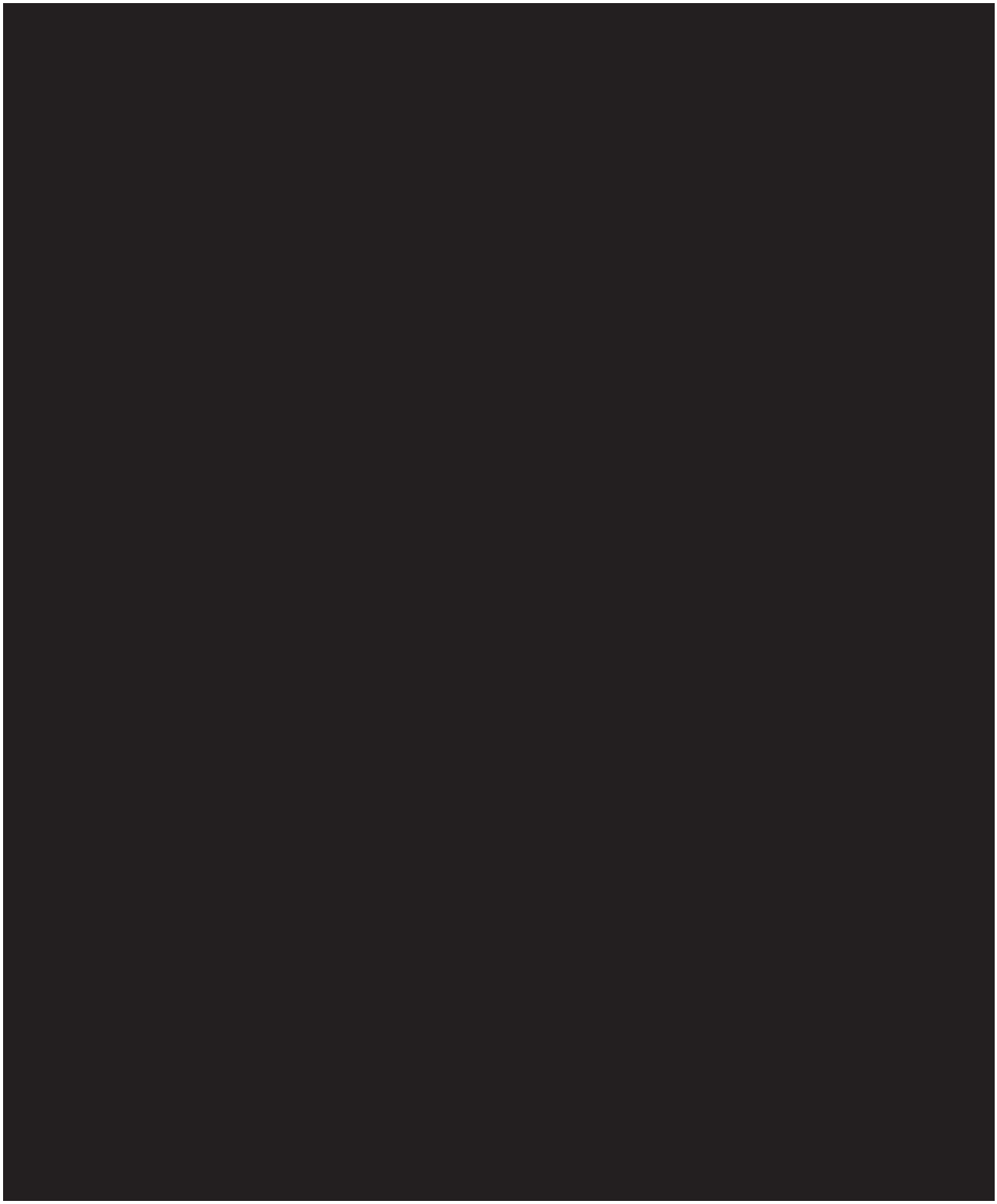
17. DOSING COMPLIANCE AND TREATMENT EXPOSURE

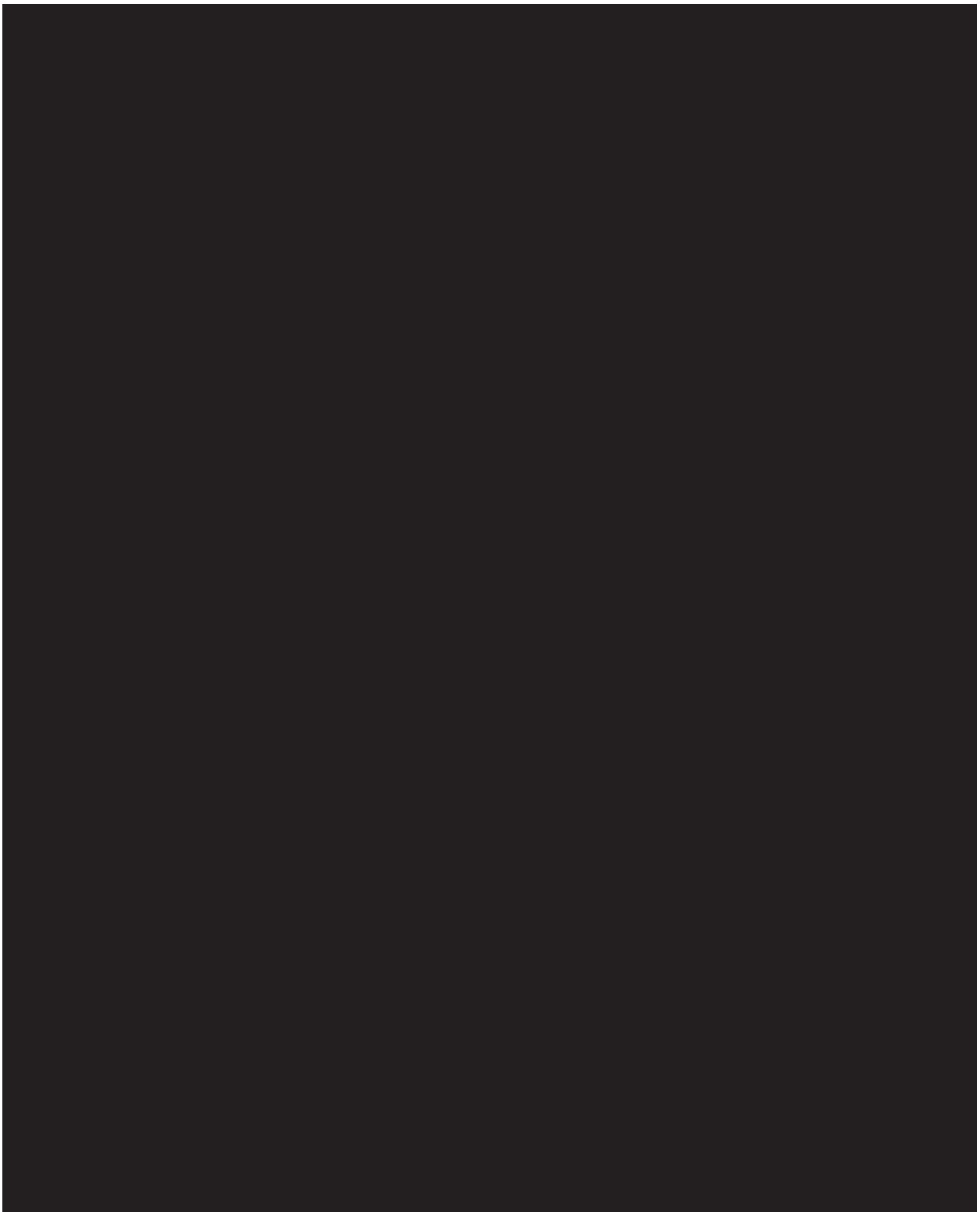
No summaries will be performed for dosing compliance or study intervention exposure. A subject listing will be provided for in-office instillations of Refresh Classic and 512 instillation variations.

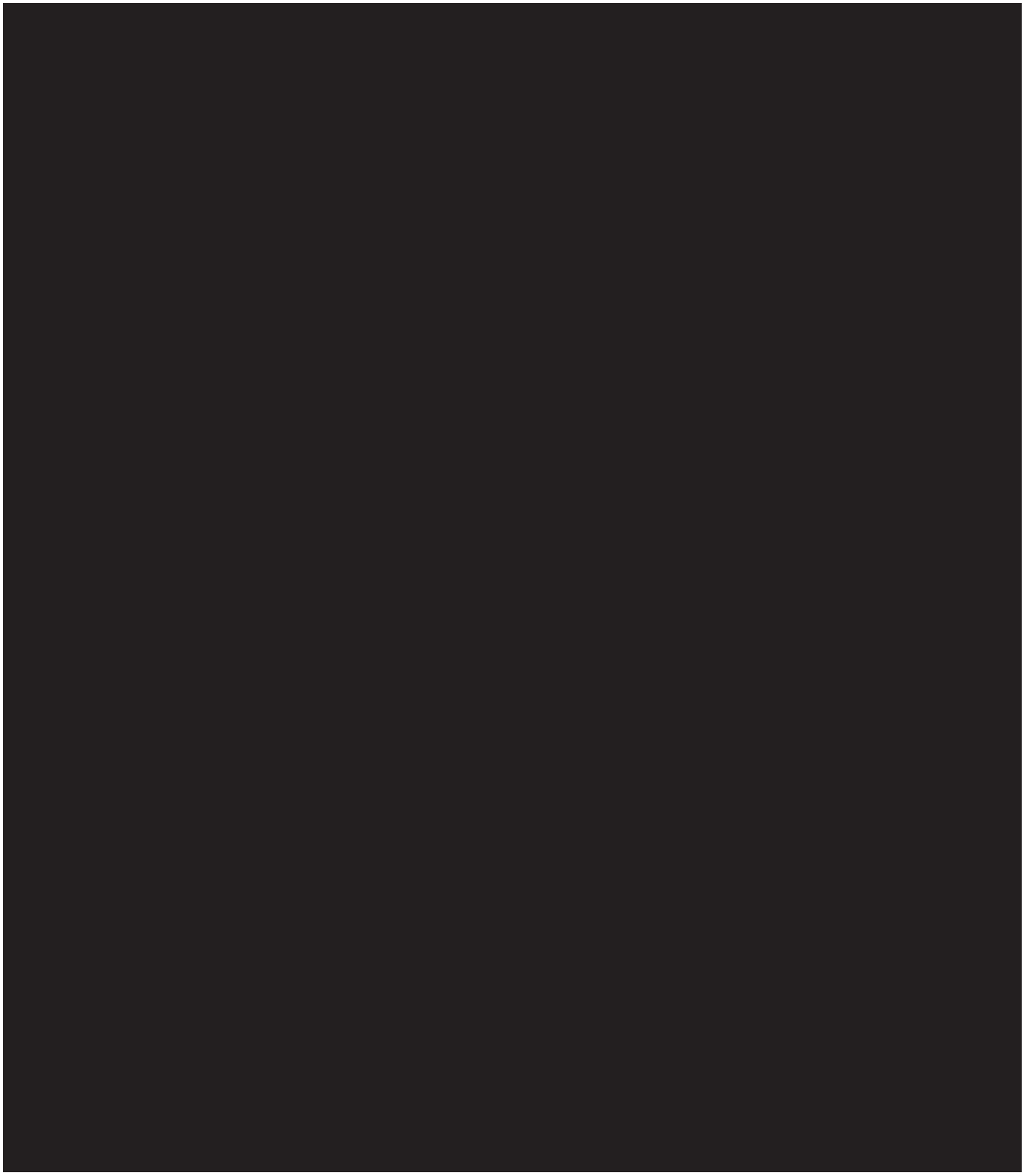


[redacted]









19. SAFETY ANALYSES

All safety analyses will be conducted using the SAF.

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 it is 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. 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, 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 study intervention (i.e., after Refresh Classic instillation). Only TEAEs will be summarized, however all AEs (for all subjects) 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 (OD, OS) 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.

A field “Most Recent Instillation Before the AE Onset” will be collected on the AE CRF with the choices of “None,” “Refresh Classic,” “Instillation Variation 1,” “Instillation Variation 2,” “Instillation Variation 3,” “Instillation Variation 4.” The choice “None” will indicate AEs starting after informed consent and before any instillation of study intervention (i.e., before Refresh Classic instillation), the choice “Refresh Classic” will indicate AEs starting after Refresh Classic instillation and before any 512 instillation variation, the choice “Instillation Variation 1” will indicate AEs starting after the first 512 instillation variation but before the second 512 instillation variation, and so on. The overall summary of TEAEs will be presented based on the answers to the field “Most Recent Instillation Before the AE Onset” for groups, “Refresh Classic” to capture all AEs with an answer “Refresh Classic,” “512 Instillation Variations” to capture all AEs with an answer “Instillation Variation 1,” “Instillation Variation 2,” “Instillation Variation 3,” or “Instillation Variation 4,” and “All Subjects” to cover all TEAEs. Given the nature of the study design, each subject can get a maximum of 5 drops of study interventions throughout the study, and a subject can have AEs reported under both “Refresh Classic” and “512 Instillation Variations.”

Ocular TEAEs will be summarized showing the number and percentage of subjects who experienced at least one ocular TEAE attributed to either Refresh Classic instillation or any 512 instillation variation, classified by MedDRA SOC and PT. Ocular TEAEs attributed to the Refresh Classic instillation are ocular TEAEs in the right eye that started after Refresh Classic instillation and before any 512 instillation variation into the right eye. Ocular TEAEs attributed to 512 instillation variation are ocular TEAEs that started after a 512 instillation and occurred in an eye with a 512 instillation

variation. 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 for the associated study intervention. In the summaries, SOCs will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Similar to overall summary of TEAEs, non-ocular TEAEs will be summarized by SOC and PT based on the answers to the field “Most Recent Instillation Before the AE Onset” under groups “Refresh Classic,” “512 Instillation Variations,” and “All Subjects.” All AEs will be presented in a subject listing.

19.2 Corrected Visual Acuity

The logarithm of the minimum angle of resolution (logMAR) CVA will be assessed in both eyes before study intervention instillation (pre-drop) and post-last drop of 512 instillation variation using an Early Treatment Diabetic Retinography Study (ETDRS) Series 2000 chart.

The observed and change from baseline (i.e., pre-drop measurement) in logMAR will be summarized for each eye (OD and OS) using continuous descriptive statistics for all subjects. A subject listing of CVA will be produced. EDC will have change from pre-drop CVA logMAR collected, which will be presented in the listing. The table summary of change from baseline will be based on calculated values.

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 in both eyes before study intervention instillation (pre-drop) and post-last drop of 512 instillation variation. The abnormal findings (or score > 0) will be graded for clinical significance (CS) and non-clinical significance (NCS).

Shift tables of score values will be provided comparing post-last drop measurements to baseline (i.e., pre-drop measurement) for OD and OS separately for all subjects. A subject listing of the slit-lamp biomicroscopy parameters will be produced.

20. INTERIM ANALYSES

No interim analysis will be performed in this study.

21. CHANGES FROM PROTOCOL-STATED ANALYSES

There are no changes from protocol-stated analyses.

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 will be planned for this study. [redacted]

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

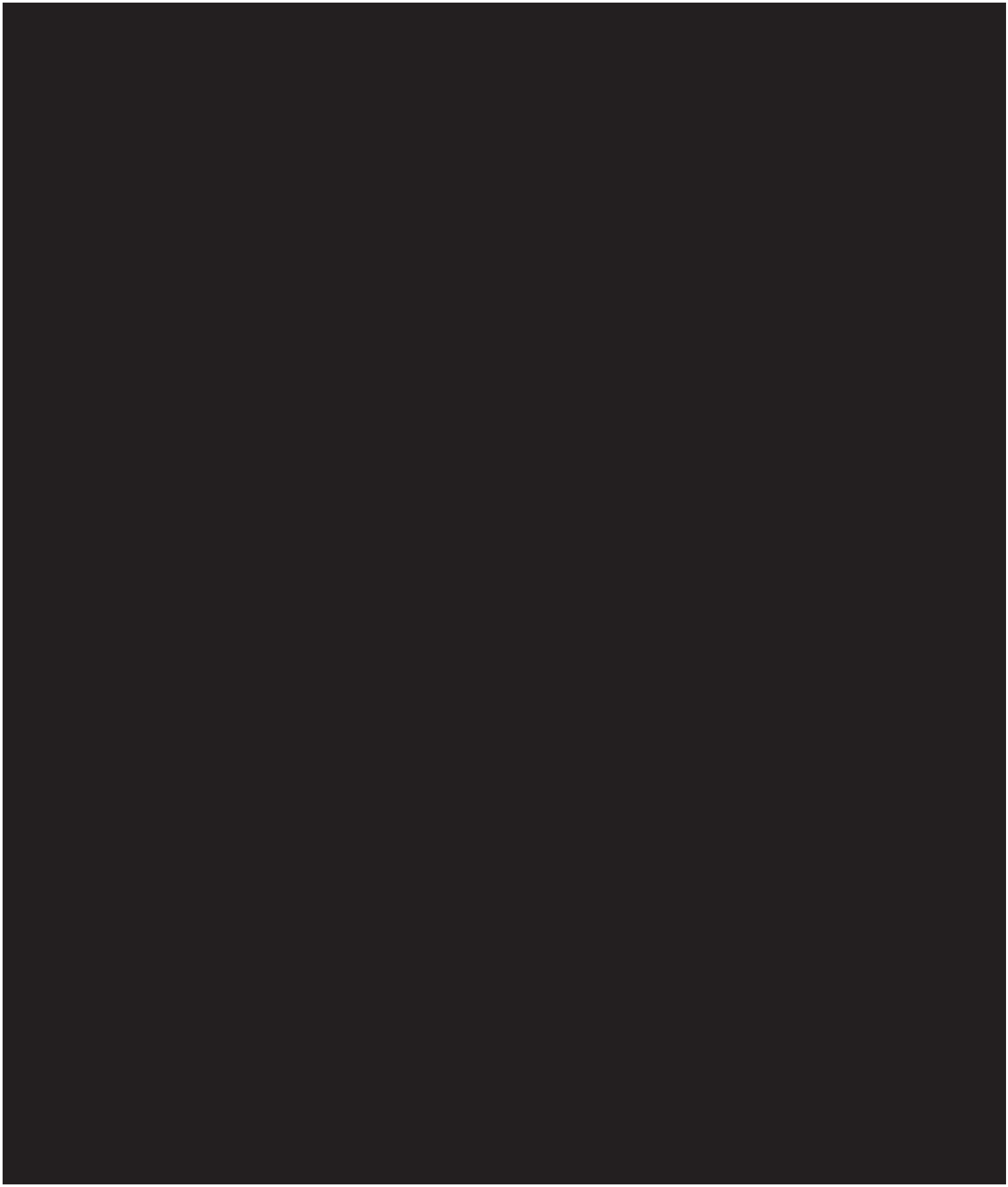
[redacted]

Number	Title	Population
[redacted]		
Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety Analysis Set
Table 14.3.1.2	Ocular Treatment-Emergent Adverse Events Attributed to Study Intervention Instillation by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.3	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
[redacted]		

23.2 Listings

Number	Title	Population
Listing 16.1.7	Screening and 512 Sequence Randomization	Randomized Subjects
Listing 16.2.1.1	Subject Disposition	All Subjects

Number	Title	Population
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	Safety Analysis Set
Listing 16.2.3	Analysis Sets	Safety Analysis Set
Listing 16.2.4.1.1	Demographics	Safety Analysis Set
Listing 16.2.4.1.2	Childbearing Potential and Pregnancy Tests	Safety Analysis Set - Female Subjects Only
Listing 16.2.4.2	Medical History	Safety Analysis Set
Listing 16.2.4.3	Prior and Concomitant Medications	Safety Analysis Set
Listing 16.2.4.4	Concomitant Procedures	Safety Analysis Set
Listing 16.2.5	In-Office Instillation of Refresh Classic and 512 Instillation Variations	Safety Analysis Set
[redacted]		
Listing 16.2.7	Adverse Events	Safety Analysis Set
Listing 16.2.8.1	Corrected Visual Acuity (CVA)	Safety Analysis Set
Listing 16.2.8.2	Slit-Lamp Biomicroscopy	Safety Analysis Set



Electronic Record and Signature Disclosure created on: 17-Nov-2021 | 11:28
Parties agreed to: Agustin Calatroni, Cecilia Chao, Michelle Senchyna, Rebecca Mestek, Ryan Thompson, Yan Liu