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STATISTICAL ANALYSIS PLAN

A Multi-Center, Double-Masked Phase 3 Evaluation of the Safety and Efficacy of LNZ101 for the Treatment of Presbyopia

Sponsor: LENZ Therapeutics, Inc.

[redacted]

Protocol Number: 22-150-0018

Author: [redacted]

Ora Inc.

Date: 12MAR2024

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SAP Date: **12MAR2024**

Statistical Analysis Plan Approval

[redacted]

[redacted]

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[redacted]

List of Abbreviations

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BCDVA	Best-Corrected Distance Visual Acuity
CI	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
FCS	Fully Conditional Specification
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
LL-BCDVA	Low-luminance Best-Corrected Distance Visual Acuity
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MNAR	Missing Not at Random
NCS	Not Clinically Significant
QD	*Quaque die* (Once Daily)
PDF	Portable Document Format
PP	Per Protocol
PRO	Patient-Reported Outcomes
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
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
WOCF	Worst Observation Carried Forward

[redacted]

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe in detail the planned analyses and reporting for protocol 22-150-0018, Amendment 4, Version 5.0 dated 31JUL2023. 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 (CSR).

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, the most recent ICH E9 (R1) Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials, and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

2. Study Objectives

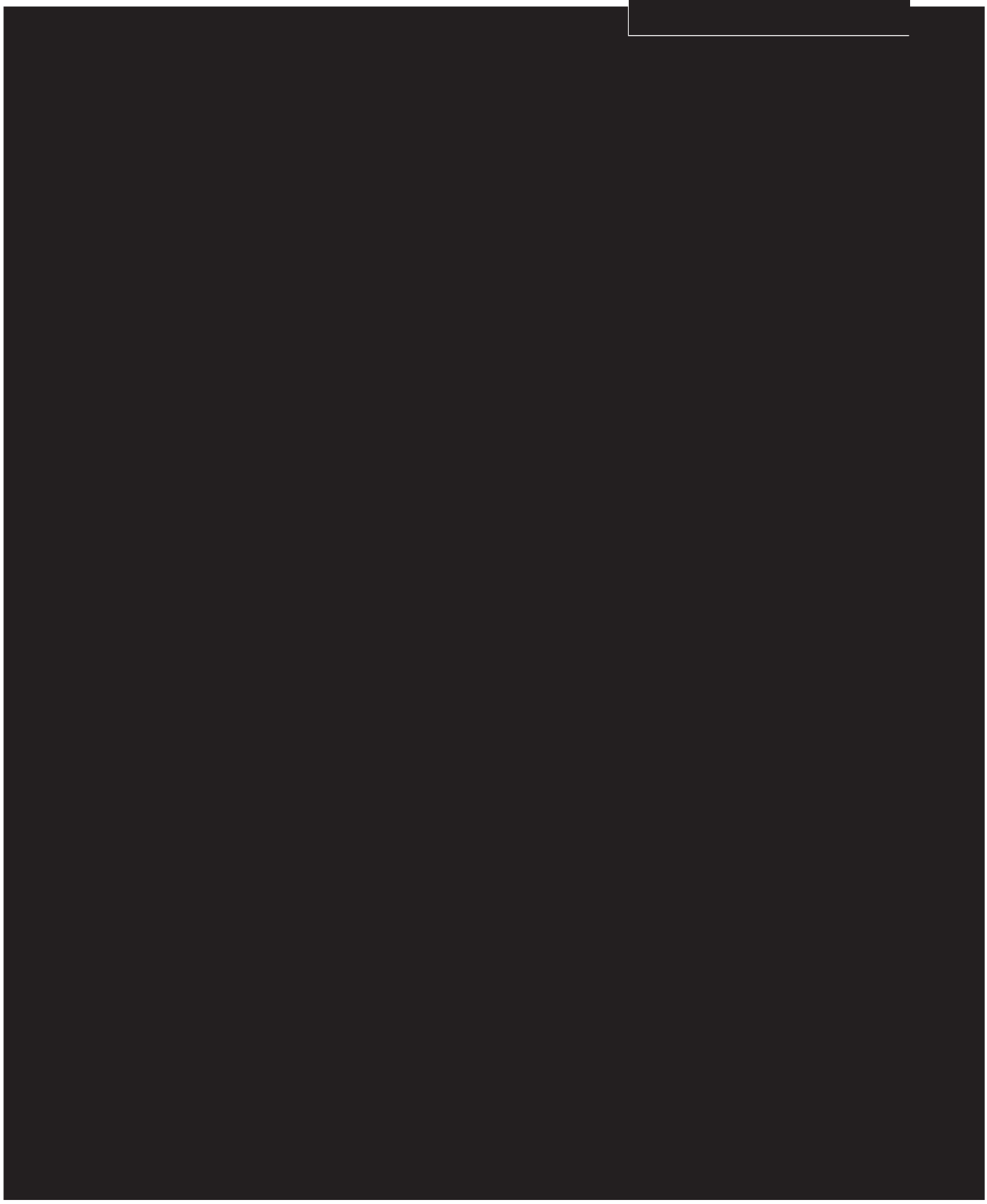
The primary objective of the study is to evaluate the safety and efficacy of LNZ101/LNZ100 compared with vehicle for the treatment of Presbyopia.

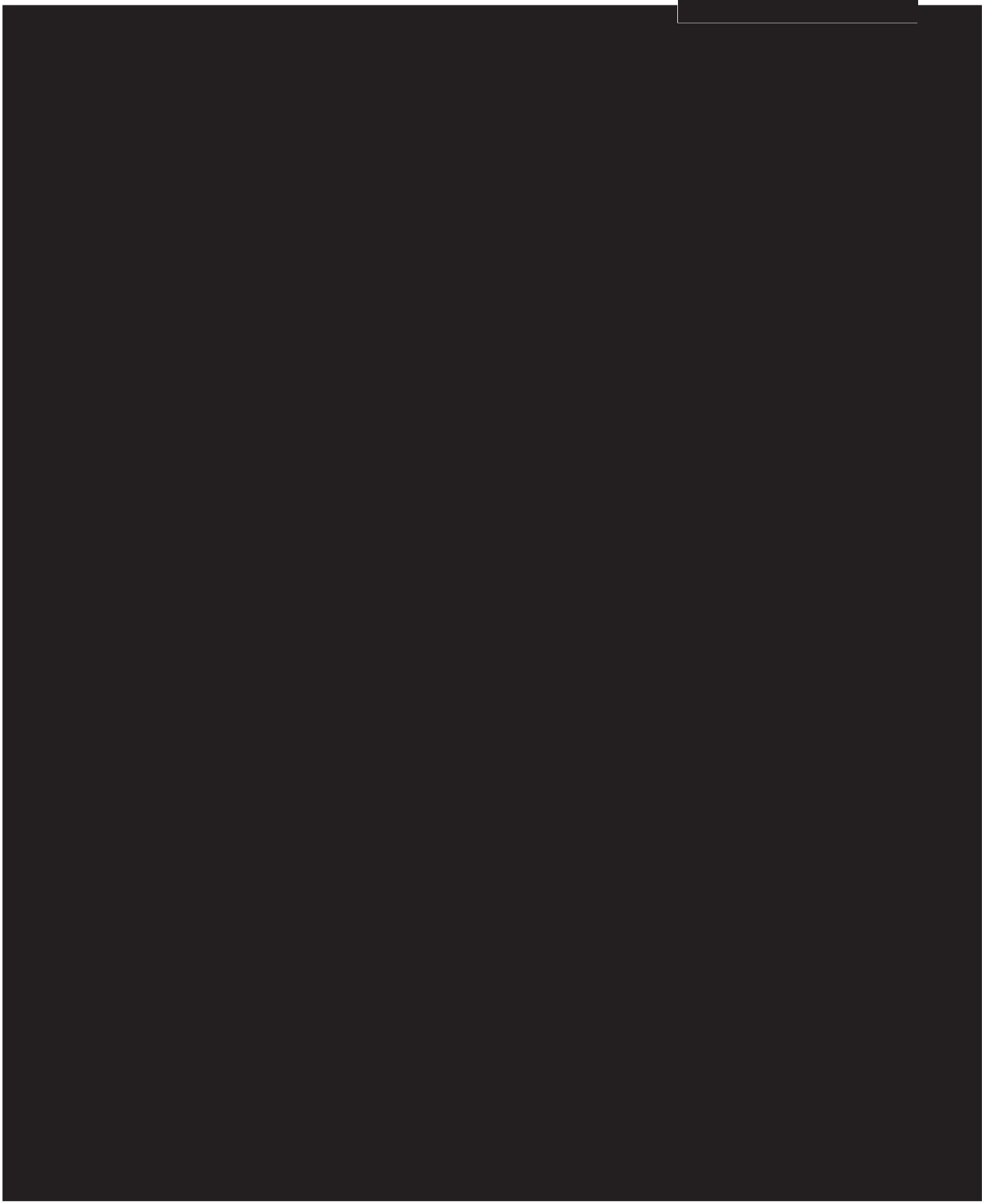
3. Study Endpoints

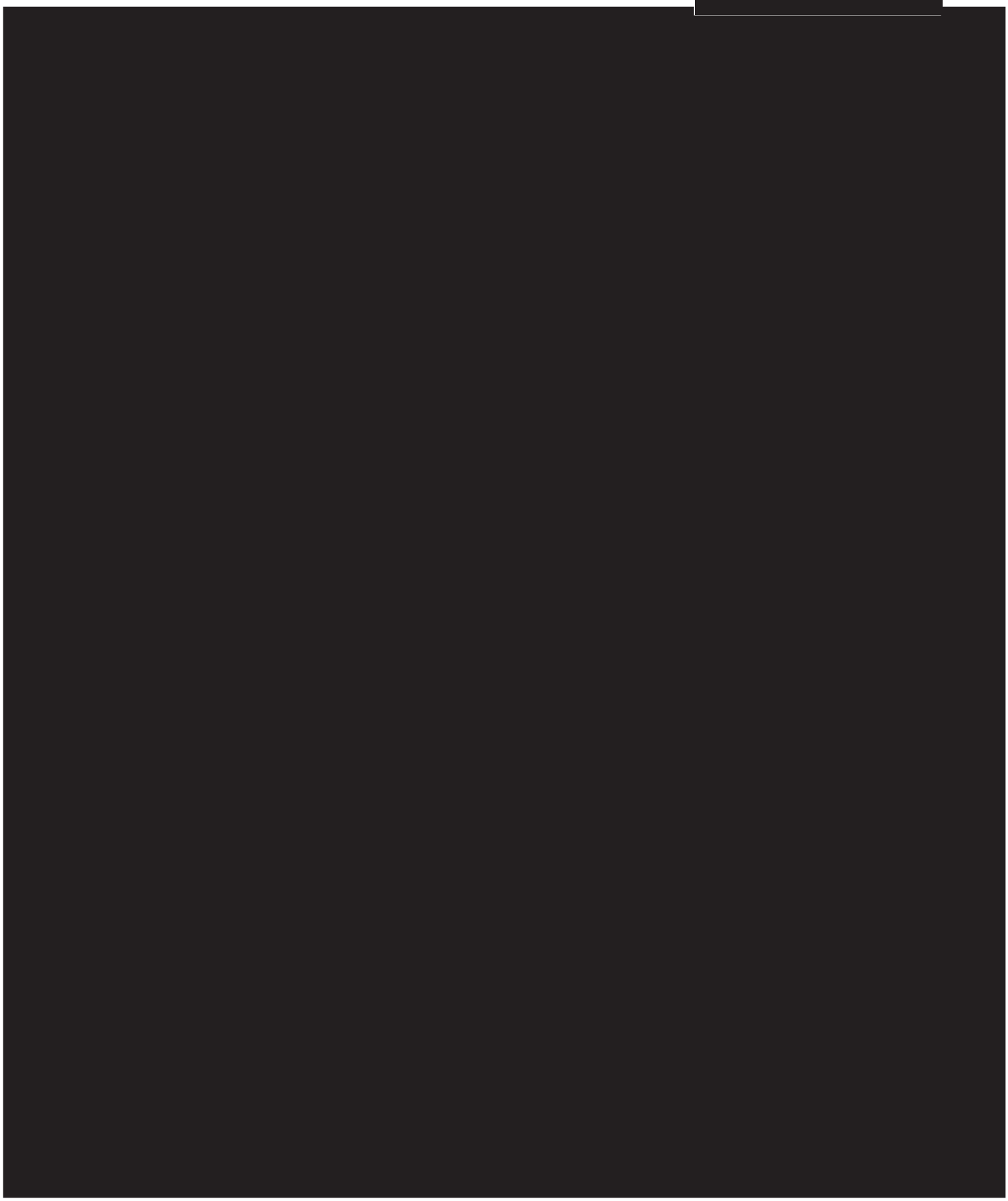
3.1 Primary Endpoints

The primary efficacy endpoint is the percentage of study eyes that achieve a 3-line (15-letter) or greater improvement from baseline in the measurement of monocular best-corrected distance visual acuity (BCDVA) at 40 cm and no loss in BCDVA ≥ 5 letters (Early Treatment of Diabetic Retinopathy Study [ETDRS] chart at 4 m) [redacted] for each LNZ treatment relative to vehicle.

[redacted]







[redacted]

3.4 Safety Variables

The safety variables include the following:

- Adverse events (AEs) (reported, elicited, and observed)

- Pregnancy test
- Monocular and binocular BCDVA at 4 m (photopic and mesopic [low-luminance])
- Slit lamp biomicroscopy
- Intraocular pressure (IOP)
- Dilated fundus exam
- Conjunctival redness score

3.5 Statistical Hypotheses

The clinical hypothesis of this study is that LNZ101/LNZ100 is superior to vehicle in improving near vision in the study eye of subjects with presbyopia.

The primary hypothesis for both treatments will be tested using Hochberg's step-up method with family-wise error rate controlled at two-sided 0.05 significance level. Further details are provided in Section 8.5.

3.6 Estimands

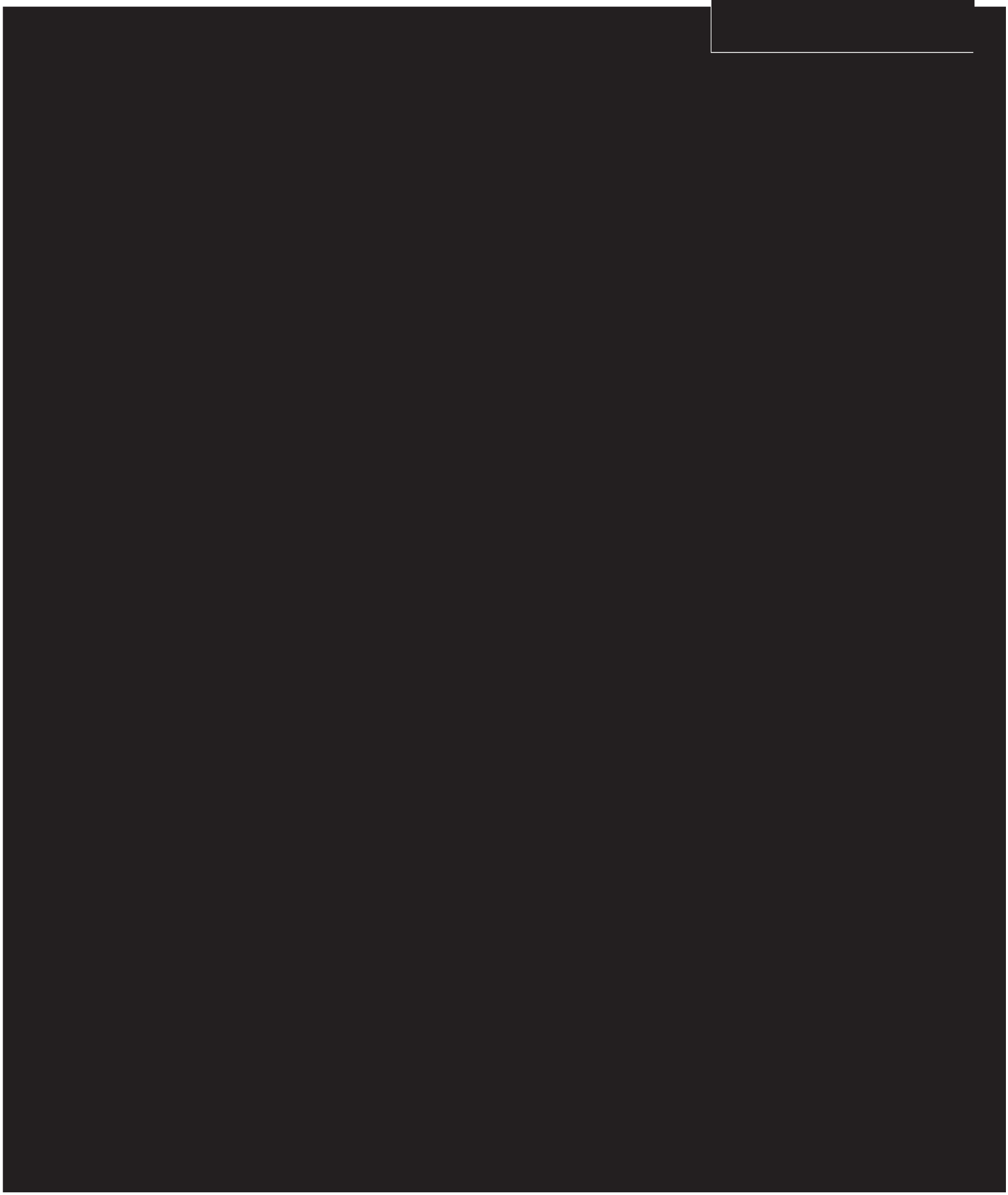
The primary comparisons in this trial will be between study eyes treated with LNZ101 versus vehicle and study eyes treated with LNZ100 versus vehicle for the Full Analysis Set (FAS) using the following estimand:

- Population: subjects with presbyopia defined through enrollment criteria
- Endpoint:
  - Percentage of study eyes that achieve a 3-line (15-letter) or greater improvement from baseline in the measurement of monocular BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4 m) for LNZ101 relative to vehicle.
  - Percentage of study eyes that achieve a 3-line (15-letter) or greater improvement from baseline in the measurement of monocular BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4 m) for LNZ100 relative to vehicle.

4. Study Design and Procedures

4.1 General Study Design

This is a randomized, double-masked, multi-center, vehicle-controlled study evaluating the safety and efficacy of LNZ101/LNZ100 compared to vehicle in approximately 222 subjects with presbyopia.



[redacted]

4.3 Study Treatments

The study treatments are as follows:

- LNZ101 [redacted]
- LNZ100 [redacted]
- Vehicle ophthalmic solution

4.3.1 Method of Assigning Subjects to Treatment Groups

Each subject who signs an informed consent form (ICF) will be assigned a subject number (a six-digit number starting with the 3-digit site number followed by a sequential three-digit number starting with 001). Once a subject meets all qualification criteria [redacted]), they will be randomized [redacted] via an interactive response technology system to 1 of 3 treatment groups (1: LNZ101 or 2: LNZ100 or 3: vehicle). Randomization will not be stratified by site.

[redacted]

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., iris color and baseline characteristics) are balanced across treatment groups, and to provide validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce the potential of bias during data collection and the evaluation of clinical endpoints.

5. Sample Size

A sample size of 222 subjects [redacted] yields >99% power to establish superiority of LNZ101/LNZ100 to vehicle in the proportion of study eyes that achieve a 3-line (15- letter) or greater improvement from baseline in the measurement of monocular BCDVA at 40 cm and no loss in BCDVA ≥5 letters (ETDRS chart at 4 m) [redacted]

6. Data Preparation

6.1 Input Data

Study data will be recorded on the electronic Case Report Forms (eCRFs) supplied by Ora Inc. (Ora) using iMednet Electronic Data Capture (EDC) system.

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, with written authorization provided by appropriate Ora and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

6.2 Output Data

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

The SDTM and ADaM versions, implementation guide versions, and Pinnacle 21 version will be documented in the respective reviewer's guides in the final CDISC package.

7. Analysis Sets

7.1 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects. No subjects will be excluded from the FAS due to protocol violations/deviations. Subjects in the FAS will be analyzed as randomized.

7.2 Per Protocol Set

The Per Protocol (PP) set will include subjects in the FAS who do not have significant protocol deviations that affect the primary endpoint analysis. The severity of protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP set will be analyzed as treated.

7.3 Safety Set

The Safety set will include all subjects who have received at least one dose of the study drug. Subjects in the Safety set will be analyzed as treated.

[redacted]

8. General Statistical Considerations

8.1 Unit of Analysis

The study eye will be used for all monocular efficacy analyses. The fellow eye will be used in binocular analyses as specified. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The Study Eye is the eye at baseline that meets all enrollment criteria, specifically.

[redacted]

All AEs and medical history will be presented at the subject level.

8.2 Missing or Inconclusive Data Handling

8.2.1 Missing Efficacy Assessments

The primary analysis will be based on MI methodology as specified in Section 3.6. All secondary endpoints of BCDVA will be analyzed similarly.

8.2.2 Missing Safety Assessments

In general, there will be no imputation of missing data other than for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. 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 medication, in which case missing day will be imputed as the first dose day of study medication.
- 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 medication, in which case missing day and month will be imputed as the first dose day and month of study medication.

- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, 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 medication, in which case missing day will be imputed as the last dose day of study medication.
- 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 medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or "Yes" 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 "No" then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

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.).

8.3 Definition of Baseline

Baseline is defined as the last measurement taken prior to the administration of first dose of study drug [redacted]. Change from baseline will be calculated as Follow-up Measure minus Baseline Measure.

8.4 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. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between active treatment group and vehicle will be calculated as, Active minus Vehicle.

Confidence intervals (CIs) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

[redacted]

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit, time point, and parameter. Listings will be presented by subject number, randomized treatment, visit, time point, and parameter as applicable.

8.5 Adjustments for Multiplicity

The primary hypothesis for both treatments (LNZ101 vs vehicle and LNZ100 vs vehicle) will be tested using Hochberg's step-up method with family-wise error rate controlled at two-sided 0.05 significance level. This procedure ranks the p-values from the least significant (largest p-value) to the most significant (smallest p-value) and examines the p-values in that order until it reaches the most significant one.

[redacted]

8.6 Prohibited Medications

The concomitant medications will be reviewed by the study team and medications that are prohibited will be flagged. [redacted]

[redacted]

[redacted]

9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers of subjects who were screened and screen failed, and the number and percentage of subjects who were randomized into the study, who are included in each population, included in each cohort, who completed the study, and who discontinued from the study. Subjects who were randomized and not discontinued from the study will be considered as study completers. Disposition will be summarized by treatment group and overall. Percentages will be based on the number of randomized subjects unless otherwise noted.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group and overall. The reasons for study discontinuation will be based on the total number of discontinuations for that treatment group and overall, and the reasons that will be summarized include: AE, lost to follow-up, investigator decision, protocol violation, study terminated by sponsor, withdrawal by subject (with subcategories of: due to an adverse event, due to lack of efficacy per subject, due to unknown reasons, and other) and other. The number and percentage of subjects whose reason for discontinuation was related to COVID-19 will also be presented by treatment group and overall. The subject disposition summary will also include the number and percentage of subjects with any protocol deviations, any minor deviations, or any major deviations by treatment group and overall.

A subject listing will be provided that includes the informed consent or reconsent date (if applicable), the date of study completion or discontinuation, and reason for premature study discontinuation.

The number and percentage of subjects with any major protocol deviations (major status decided by the study team at the conclusion of the study prior to database lock and unmasking) will be summarized by treatment group and overall for the Safety set. The protocol deviation categories (codes) that will be summarized include: informed consent, inclusion/exclusion and randomization, test article/study drug instillation, improper protocol procedures at site (missed, repeated, not per protocol), site's failure to report serious adverse event (SAE)/AE, visit out of window (missed, early, late), subject's non-compliance with test article, subject's use of prohibited concomitant medication, subject's failure to follow instructions, and other. A subject listing will be provided that includes the start date of the deviation, the deviation code, deviation description, action taken, whether the deviation was required to be reported to the Investigational Review Board (IRB) (and if yes, the date reported to the IRB), the classification of whether the deviation was judged to be major or minor, and whether the deviation caused the subject to be excluded from the PP Set.

Listings will also be provided for the randomization schedule, cohort assignments, screen failures, and inclusion/exclusion criteria.

10. Demographics and Baseline Characteristics

10.1 Demographics

The demographic variables collected in this study include date of birth, age, sex at birth, childbearing potential for female subjects, race, ethnicity, and iris color (of the right and left eyes). Subjects who record more than one race will be grouped into a single category denoted as Multi-racial. Demographic variables will be summarized for the FAS and Safety set, separately.

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

A subject listing that includes all demographic variables will be provided.

[redacted]

11. Medical History and Concomitant Medications

Listings of medical history, concomitant medications, and concomitant procedures will be generated separately. Medical history and concomitant medications will also be listed separately for ocular and non-ocular data.

11.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1.

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the FAS. Ocular medical history will be similarly summarized at the subject level. [redacted]

11.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global, B3, September 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 drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug.

Concomitant medications will be summarized using the FAS. Medications will be tabulated for each treatment group and overall, using number and percentage of subjects. Subjects may have more than one medication per ATC class. 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 ordered by descending frequency based on all subjects.

[redacted]

11.3 Concomitant Procedures

Concomitant procedures will be coded using MedDRA Version 25.1. Concomitant procedures will be listed but not summarized.

12. Dosing Compliance

In addition to the analyses described in the following sections, subject listings will be provided for placebo and study drug assignment, dispensation, and instillation, as well as dosing diary dispensation and collection.

12.1 Dosing Compliance

Subjects will be provided with a dosing diary to document once daily (QD) dosing. Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

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

The number of actual doses received will be calculated by counting the number of used ampoules in the Study Drug Accountability eCRF along with the number of doses instilled in-office on the Study Drug Instillation eCRF across all visits. [redacted]

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group using the FAS and Safety set. The compliance category defined above will be summarized with discrete summary statistics.

Study drug accountability will also be displayed in a subject listing.

13. Efficacy Analyses

13.1 Primary Analysis of Primary Efficacy Variable

The primary efficacy endpoint in this study is the percentage of study eyes that achieve a 3-line (15-letter) or greater improvement from baseline in the measurement of monocular BCDVA at 40 cm and no loss in BCDVA ≥ 5-letters (ETDRS chart at 4 m) [redacted]

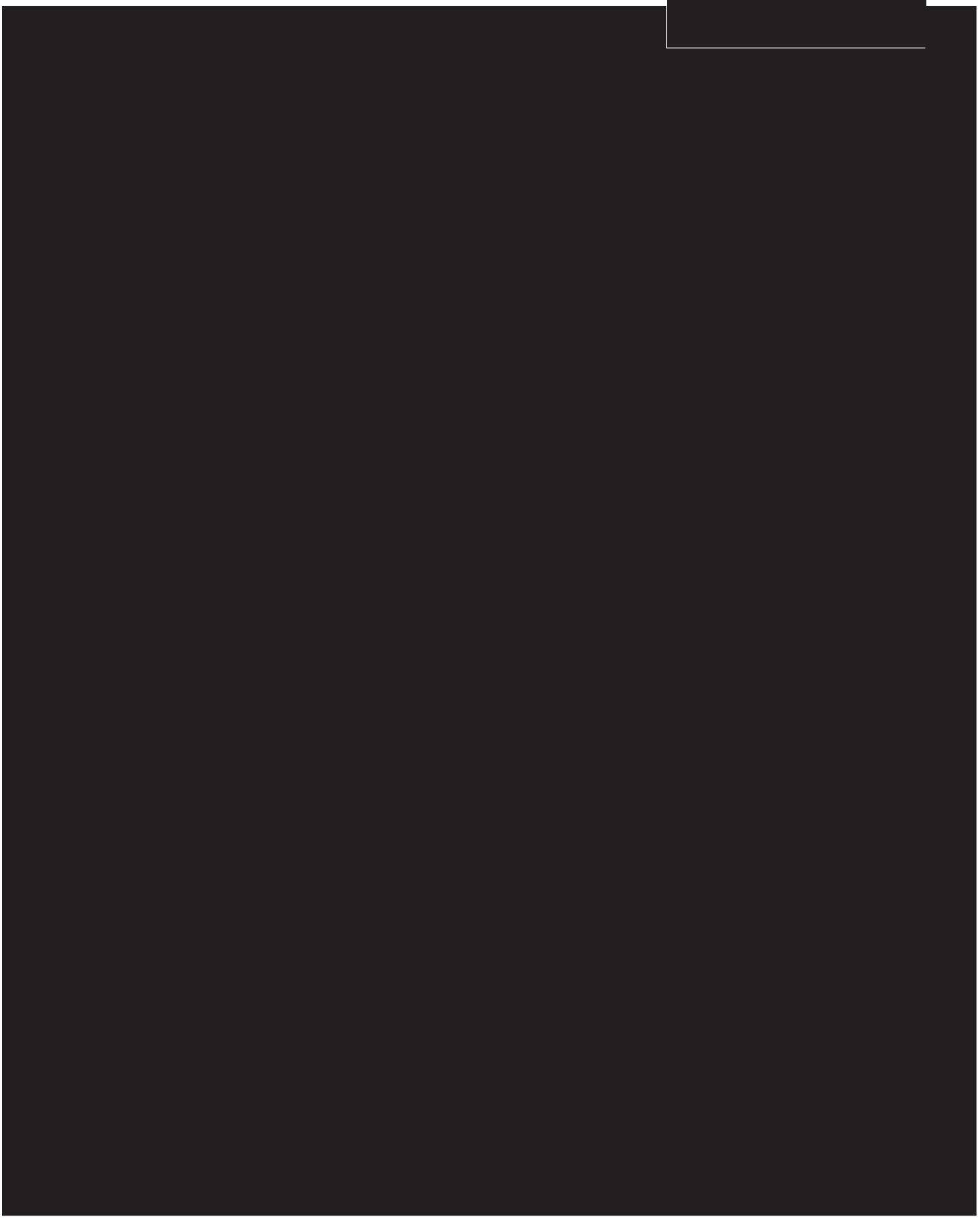
[redacted]

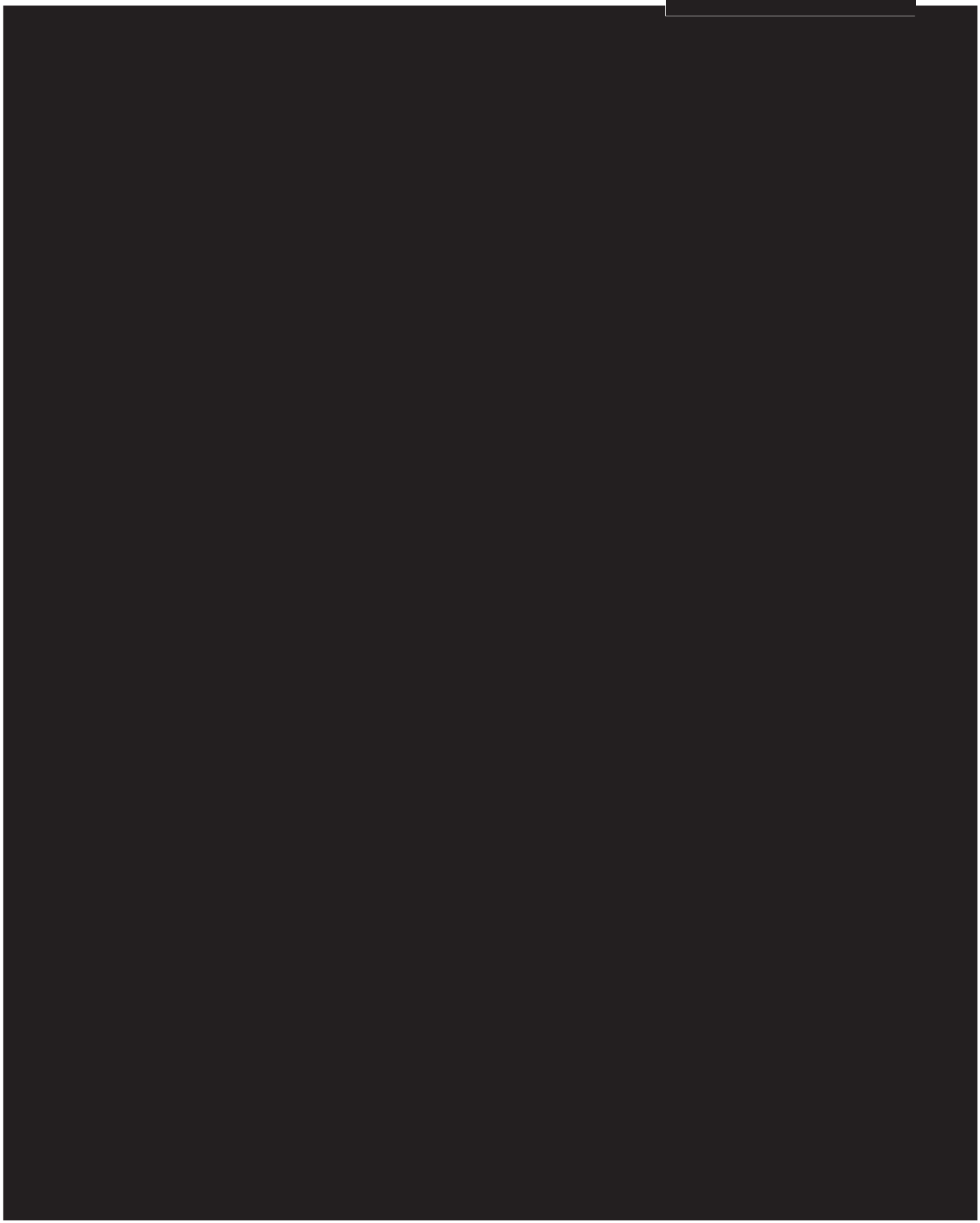
Descriptive statistics will be presented by treatment group. Testing of the primary endpoint will be completed using logistic regression with treatment as the fixed effect and baseline BCDVA at 40 cm as a covariate. The adjusted odds ratios and marginal proportions and differences in proportions along with corresponding two-sided 95% CIs and p-values will be presented.

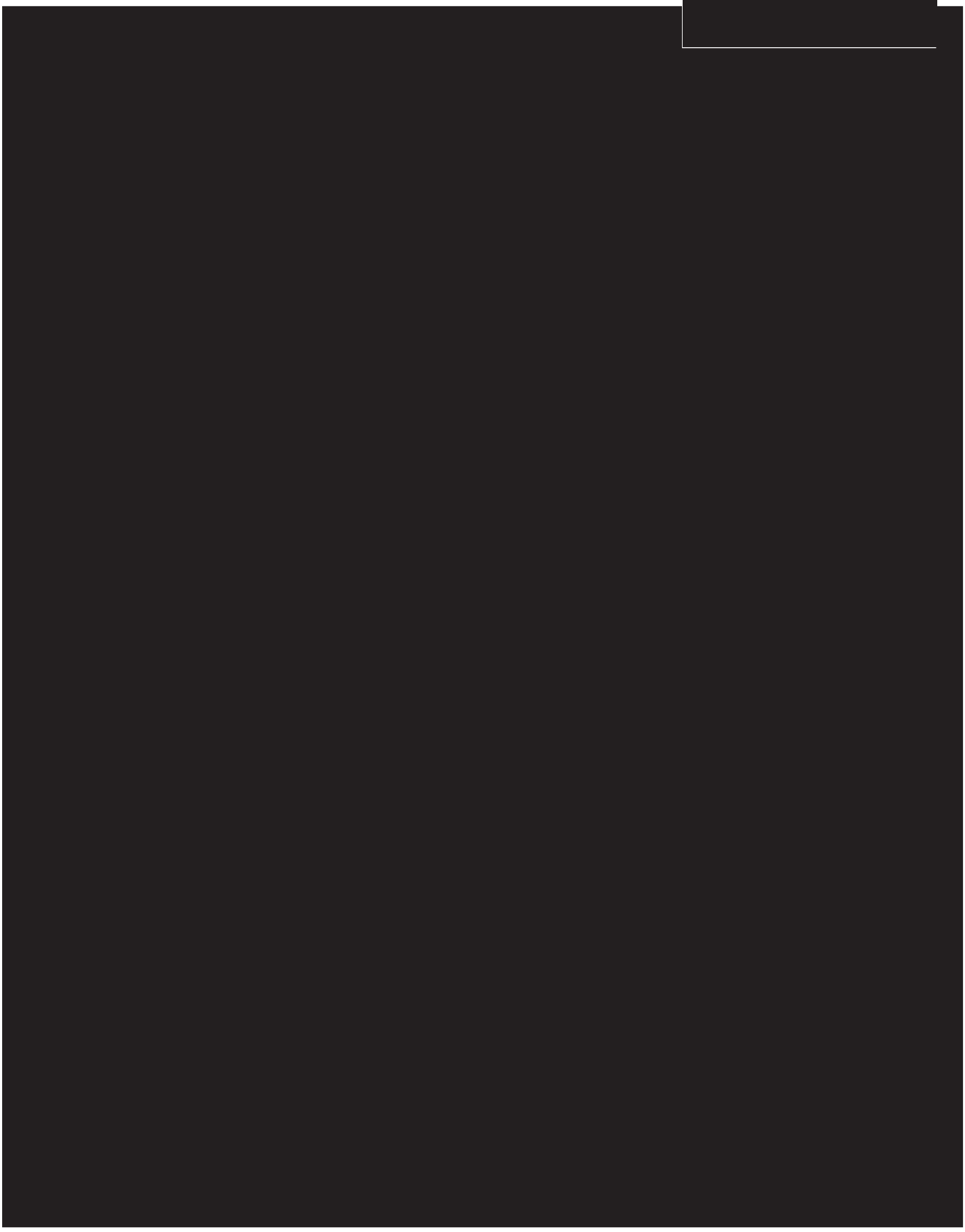
Treatment comparisons will also be made using Pearson's Chi-square test. The p-values from Pearson's Chi-square test will be presented. The differences in proportions along with corresponding two-sided 95% CIs based on asymptotic normal distribution will also be presented.

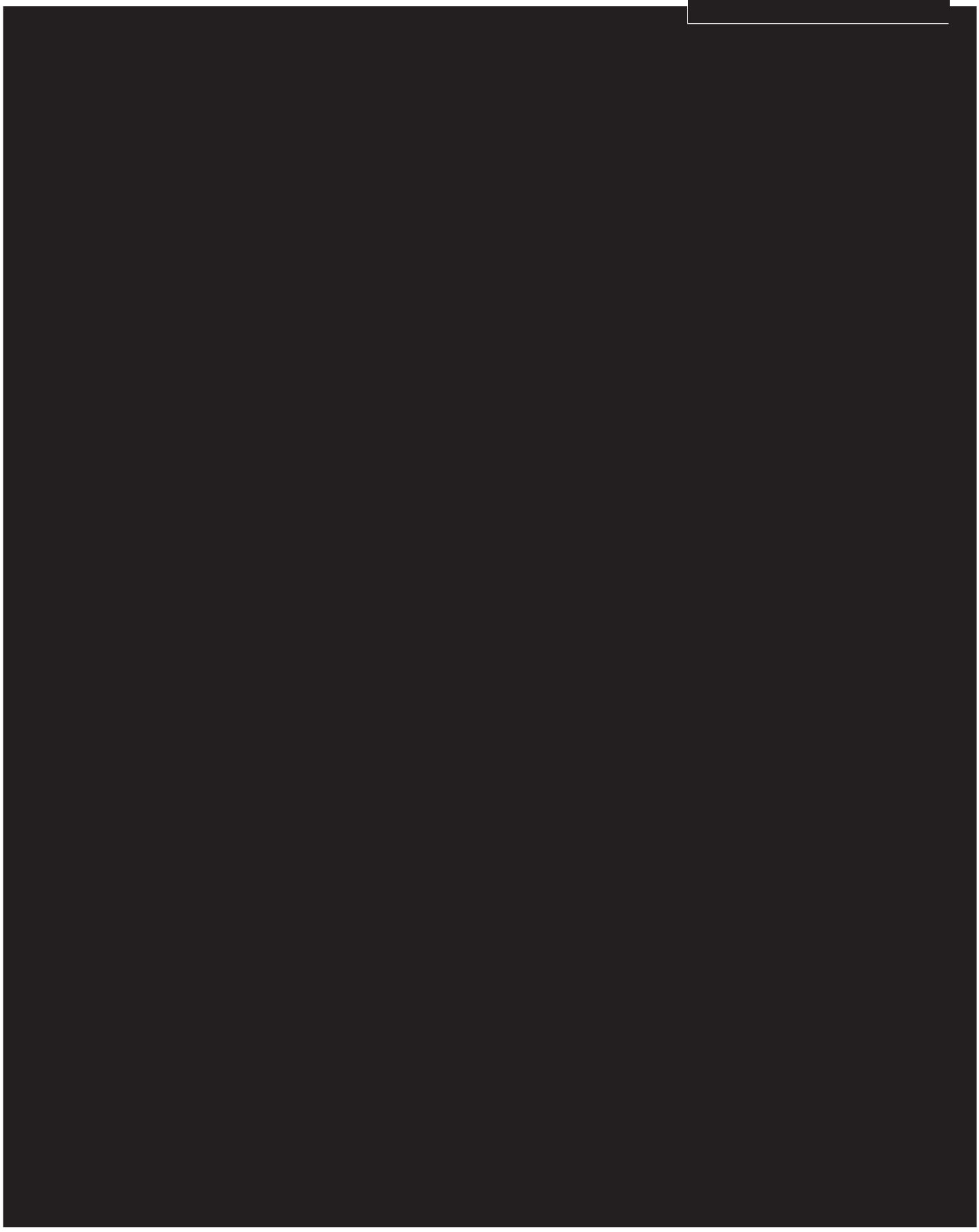
[redacted]

[redacted]









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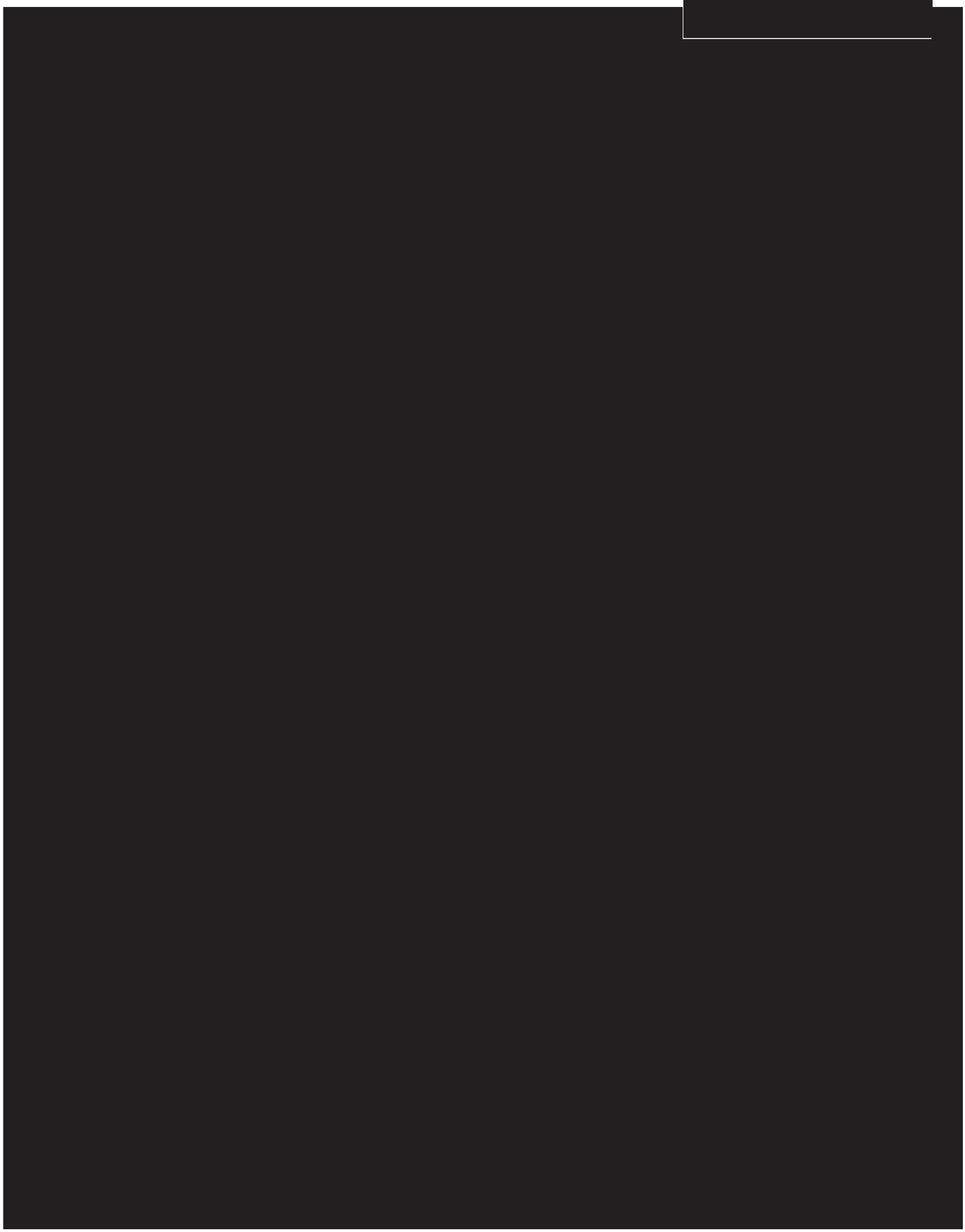
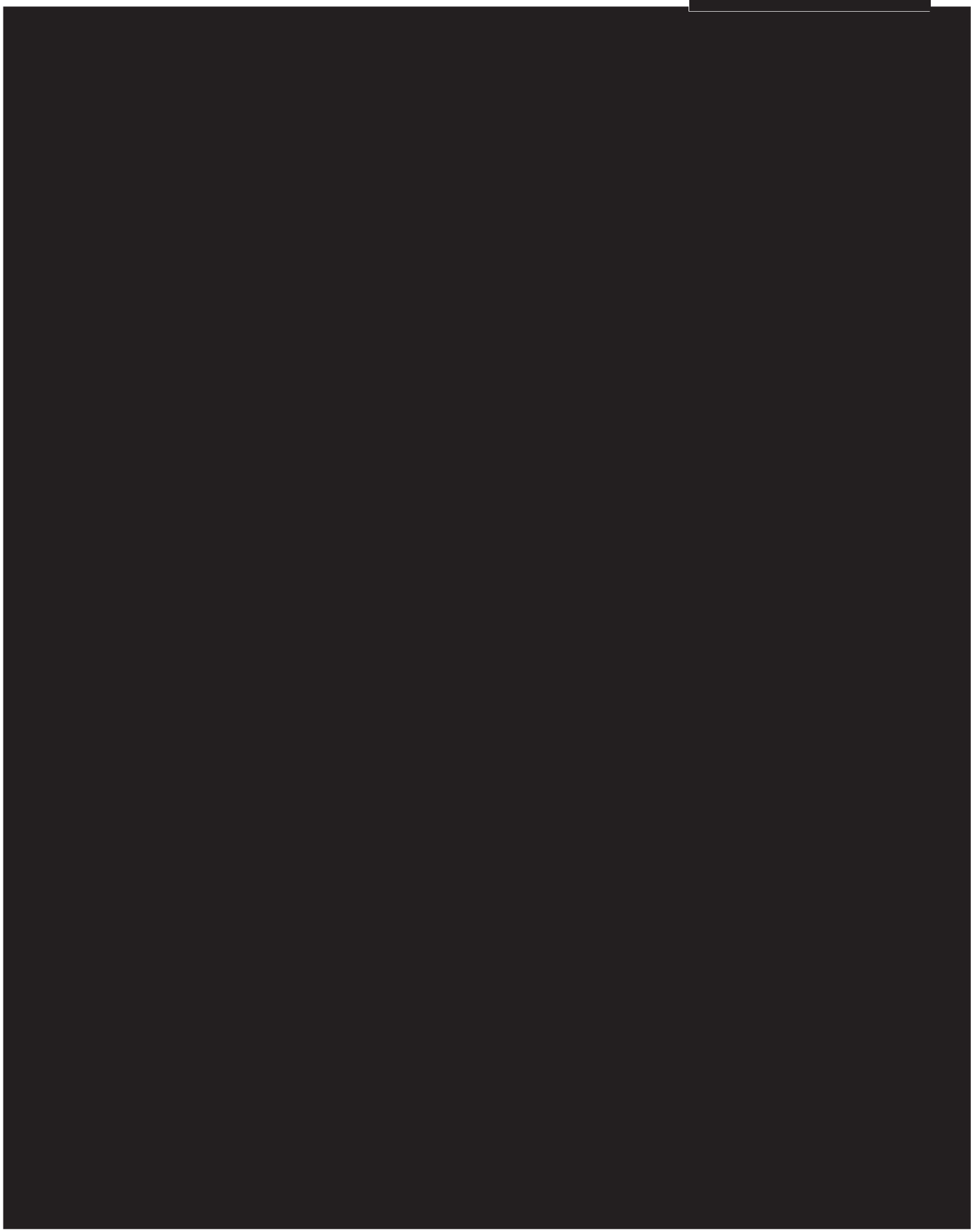
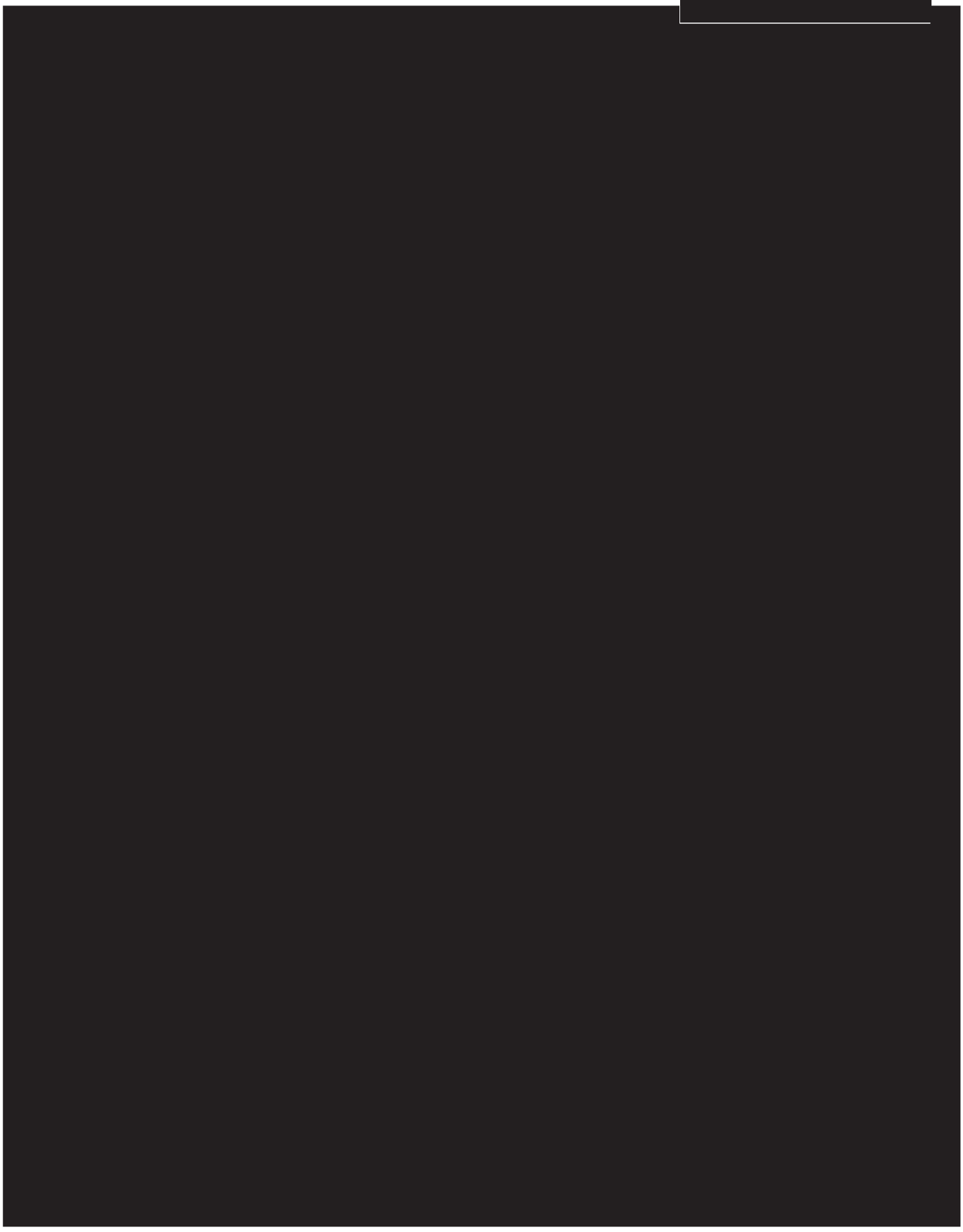
13.2 Sensitivity Analysis of Primary Efficacy Variable(s)

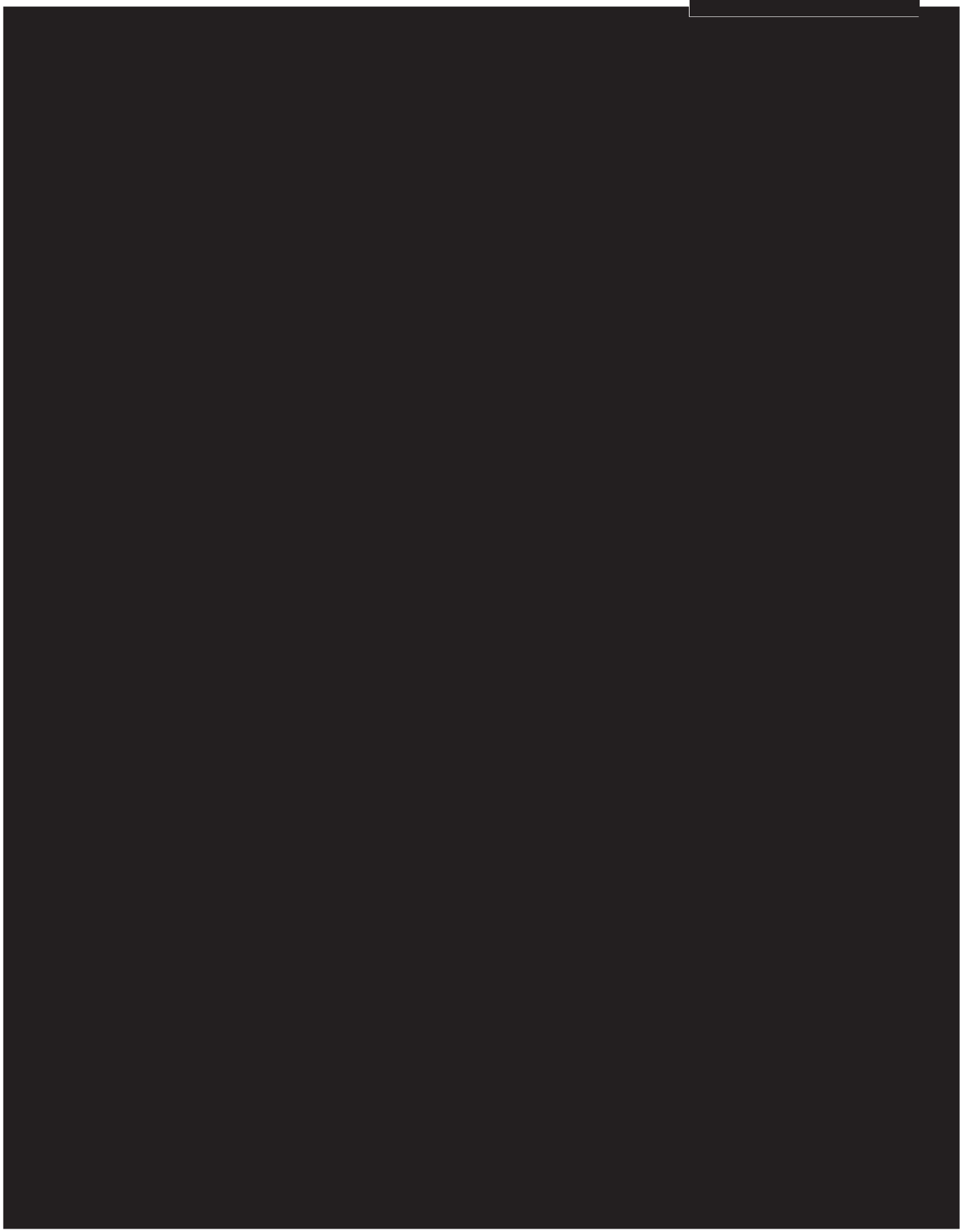
The following sections describe the sensitivity analyses that will be completed for the primary endpoint.

[redacted]









14. Safety Analyses

All safety analyses will be conducted using the Safety set.

14.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an investigational product (IP) in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g. off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. All AEs will be collected from the time a subject signs the ICF through the subject's study exit. Study drug includes the investigational drug under evaluation and vehicle given during the study. All AEs will be coded using the MedDRA Version 25.1.

Treatment-emergent adverse events (TEAE) are defined as AEs with a start date on or after the first dose of the study drug or that worsened following administration of the study drug. Adverse events recorded in the eCRF which began prior to first dose will not be included in the summary tables but will be included in the AE data listings.

Severity of an AE 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 assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate:* Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

The relationship of each AE to the study drug should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the study drug caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the study drug caused the AE.

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 by treatment group. This summary will also include breakdowns of TEAEs further categorized as ocular and non-ocular TEAEs, treatment-emergent serious adverse events (TE-SAEs), treatment-related TEAEs, treatment-related TE-SAEs, TEAEs leading to early treatment discontinuation, TEAEs leading to death, and ocular and non-ocular TEAEs by maximum severity.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE by treatment group. Ocular and non-ocular TEAEs will be summarized separately by treatment group 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 summary, SOCs and PTs within a SOC will be ordered in descending frequency of all subjects.

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

- Ocular TEAEs
- Non-ocular TEAEs
- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs
- Expected TEAEs
- Unexpected TEAEs
- Ocular TE-SAEs
- Non-ocular TE-SAEs
- Ocular TEAEs by Maximum Severity
- Non-Ocular TEAEs by Maximum Severity

All AEs will be presented in a subject listing. The AEs leading to study drug discontinuation will be listed separately. In addition, all SAEs will be presented in a separate listing.

14.2 Low-Luminance Best-Corrected Distance Visual Acuity

Monocular and binocular low-luminance best-corrected distance visual acuity (LL-BCDVA) using an ETDRS chart calibrated for testing at 4 m is conducted. Results will be recorded in logMAR units. If a subject is unable to read any letters, the subject will be asked to count fingers (with distance recorded), recognize hand movement, or perceive light perception.

The observed and change from baseline LL-BCDVA will be summarized for each eye (study eye and fellow eye for monocular LL-BCDVA) and both eyes (for binocular LL-BCDVA) using continuous descriptive statistics by time point for each treatment group. A subject listing of LL-BCDVA will also be produced.

14.3 Slit Lamp Biomicroscopy Examination

A slit lamp biomicroscopy examination will be conducted [redacted]. The results will be graded as normal, abnormal (not clinically significant [NCS]), or abnormal (clinically significant [CS]).

A table will summarize the results [redacted]. Percentages will be based on the number of subjects in each treatment group with non-missing values for the parameter at that visit. Shift tables and data listings will also be provided.

14.4 Intraocular Pressure

Intraocular pressure is measured [redacted]. Observed and change from baseline IOP values will be summarized by treatment group for the study and fellow eye separately, using continuous descriptive summary statistics in a table. The data for IOP examinations will be presented in a listing.

14.5 Dilated Indirect Fundoscopy

Dilated fundoscopy will be conducted [redacted] The results will be graded as normal, abnormal (NCS), or abnormal (CS).

A table will summarize results [redacted]. Percentages will be based on the number of subjects in each treatment with non-missing values for the parameter at that visit.

A shift table for the dilated fundoscopy parameters will also be provided [redacted].

The dilated fundoscopy results will be presented in a listing.

14.6 Conjunctival Redness

Conjunctival redness is measured [redacted]

[redacted] Conjunctival redness will be scored on a 0 to 4 scale (with whole values only), where higher scores indicate greater redness.

Conjunctival redness will be summarized [redacted]). The data for conjunctival redness will be presented in a listing.

14.7 Urine Pregnancy Test

Female subjects of childbearing potential will have a urine pregnancy test performed before treatment [redacted]. A subject-level listing by visit will be produced.

15. Other Analyses

15.1 Patient-Reported Outcome Questionnaire

Subjects will be answering a Patient Reported Outcome (PRO) questionnaire [redacted]t. Number and percentage of subjects for the responses to only the following questions will be presented by treatment group using the Safety and Per-Protocol set.

[redacted]

- [redacted]

[redacted]

- [redacted]

A subject listing will be provided for the PRO Questionnaire results.

15.2 Dark-Adapted Pupillometry

The pupil diameter (mm) [redacted] will be assessed with dark-adapted pupillometry [redacted]

The observed and change [redacted] will be summarized by treatment group [redacted], using continuous descriptive summary statistics on the Safety set.

A subject listing will be produced for dark-adapted pupillometry results.

15.3 Drop Instillation Assessment

Study drug will be instilled

A subject listing of drop instillation assessment scores will also be produced.

16. Interim Analyses

There are no interim analyses planned for this study.

17. Changes from Protocol-Stated Analyses

1. For BCDVA at 66 cm, the protocol mentions percentage of subjects who achieved no improvement, a 1-line (5-letter) or greater, 2-line (10-letter) or greater, and 3-line (15-letter) or greater improvement from pre-treatment by 1-letter increments as an exploratory endpoint. Instead of 1-letter increment, the SAP summarizes by 5-letter increments. There will not be a summary conducted on subjects who achieved no improvement.

[redacted]

18. References

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

19. Revision History

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

[redacted]