STATISTICAL ANALYSIS PLAN

A Multicenter, Double-Masked Evaluation of the Safety and Effectiveness of [redacted] (LNZ101) and [redacted] (LNZ100) in the Treatment of Presbyopia

Sponsor: LENZ Therapeutics, Inc.

[redacted]

Protocol Number: 21-100-0007

Author: [redacted]

Statistics & Data Corporation

Date: 29SEP2022

Version: 1.0

A Multicenter, Double-Masked Evaluation of the Safety and Effectiveness of [redacted] (LNZ101) and [redacted] (LNZ100) in the Treatment of Presbyopia

Protocol Number: **21-100-0007**

SAP Version: 1.0

SAP Date: **29SEP2022**

Statistical Analysis Plan Approval

[redacted]

Table of Contents

[redacted]

[redacted]

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BCDVA	Best-Corrected Distance Visual Acuity
BID	*Bis in die* (Twice Daily)
CI	Confidence Interval
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCS	Not Clinically Significant
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RDC	Remote Data Capture
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol 21-100-0007, version 4.0.0 dated17JUN2022.

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 and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

To evaluate the safety and efficacy of [redacted] (LNZ101) compared with [redacted] (LNZ100) and vehicle in the treatment of presbyopia..

2.1 Study Variables

2.2 Primary Variables

The primary efficacy variables are the following:

- Percentage of subjects who achieve a 3-line (15-letters) or greater improvement from pre-treatment in the measurement of [redacted] monocular best-corrected distance visual acuity (BCDVA) at 40 cm and no loss in BCDVA ≥ 5 letters (Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 m) [redacted]

[redacted]

[redacted]

2.5 Safety Variables

The safety variables include the following:

- Loss of BCDVA
- Low-luminance BCDVA
- Slit-lamp biomicroscopy and fundoscopy
- Conjunctival redness[redacted]
- Intraocular pressure (IOP)[redacted])
- Adverse Events (reported, elicited, and observed)

[redacted]

2.7 Statistical Hypotheses

The clinical hypothesis is that LNZ101 is non-inferior to LNZ100 and superior to vehicle in improving near vision in subjects with presbyopia. Additional hypothesis for this study is LNZ101 also improves efficacy duration in comparison to LNZ100.

3. Study Design and Procedures

3.1 General Study Design

This is a [redacted] randomized, double-masked, multi-center, crossover study evaluating the safety and efficacy of an [redacted] (LNZ101) compared with [redacted] (LNZ100) and vehicle in approximately 60 subjects with presbyopia. [redacted]

[redacted] subjects will receive one of the following treatments based on the randomized sequence they are assigned to at Visit 1:

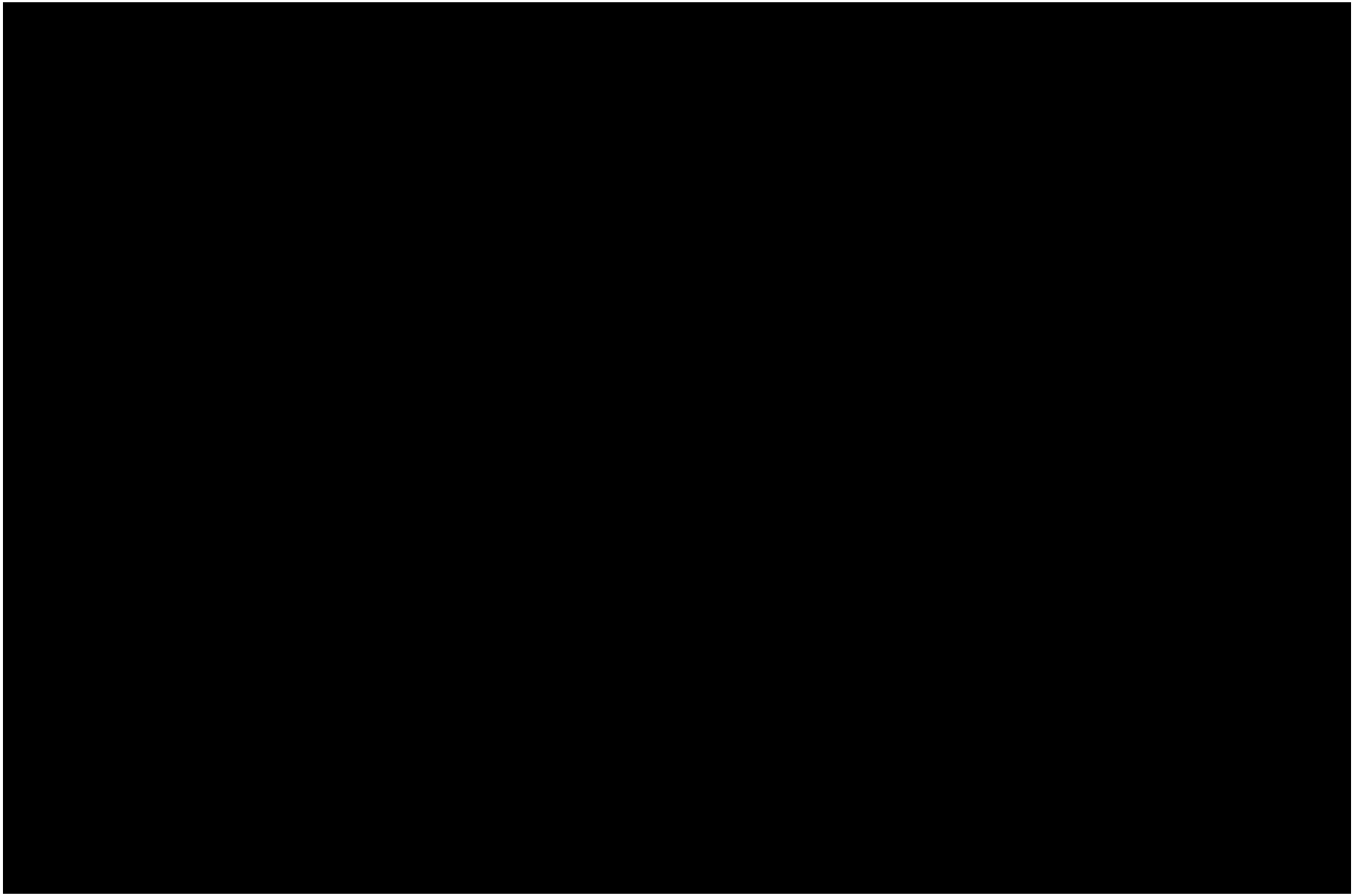
- [redacted] (LNZ101) administered bilaterally [redacted]
- [redacted] (LNZ100) administered bilaterally [redacted]
- Vehicle (non-preserved) ophthalmic solution administered bilaterally [redacted]

All subjects will receive each treatment once (crossover study design).

Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Table 1 shows the scheduled study visits, their planned study day, and the acceptable visit window for each study visit:

3.2 Schedule of Visits and Assessments

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



4. Study Treatments

The study treatments are as follows:

- LNZ101 [redacted]
- LNZ100 [redacted]
- Vehicle (non-preserved) ophthalmic solution

The two active ingredients [redacted] have been formulated and will be provided in a sterile container.

A third solution, vehicle ophthalmic solution, will be provided for the vehicle treatment in a sterile container. The formulation composition will be identical to that of the [redacted] ophthalmic solution except it will not contain any active ingredient.

4.1 Method of Assigning Subjects to Treatments

Each subject who signs an informed consent form will be assigned a screening number. Screening numbers will be assigned in sequential order beginning with 001. Once a subject meets all qualification criteria, he/she will be randomized in a 1:1:1 ratio to one of three Latin square design sequences [(1,2,3), (2,3,1), and (3, 1, 2)] detailing the order in which treatments (1: LNZ101, 2: LNZ100, 3: vehicle) will be administered over the three study visits and will be assigned a 4-digit subject number. Subject numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted. 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., demographics and baseline characteristics) are evenly balanced across treatments, and to enhance the validity of statistical comparisons across treatments. Masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

To ensure there are 40 evaluable subjects per treatment arm in the mITT (modified Intent-to-Treat) population (defined in Section 7.1), an unmasked statistician will monitor mITT qualification criteria and provide a recommendation regarding how many additional subjects to enroll into the study. The unmasked statistician will only evaluate pre-treatment monocular BCDVA at 40 cm [redacted] to make recommendations about the number of subjects to enroll.

A masked trained study technician will be instructed to administer the appropriate bottle of study drug [redacted] that corresponds to the assigned subject number according to the randomization list.

4.2 Masking and Unmasking

An independent biostatistician who is not otherwise involved in the trial will generate the complete randomized study drug kit list. The subject, Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the study.

In order to maintain masking to the study drug administrator and study subject, the LNZ101, LNZ100, and vehicle treatments will be prepared in sterile containers having an identical appearance. The sterile containers will be identical in size and color and have identical clinical labels (except for the subject number and Visit number).

When medically necessary, the Investigator may need to determine what treatment has been assigned to a subject. When possible (e.g., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking the investigational product. A two-panel clinical label with scratch-offs will be used for unmasking.

5. Sample Size and Power Considerations

This study is expected to complete at least 40 evaluable subjects in each treatment within the mITT Population. This sample size was informed with results from the previous Phase 2b study comparing Aceclidine and an Aceclidine/Tropicamide combination product to Vehicle. Power was estimated using the exact sign test of equality of paired proportions procedure in nQuery Advisor® 7.0 across a range of estimated response discordance between the treatments. The significance level of the primary analyses will be set at two-sided alpha levels of 0.10. The analyses will be considered descriptive and used to inform on future studies.

For the primary endpoint analysis at 1-hour post-dose, this sample size would provide ≥ 91% power to detect a significant treatment effect, assuming at least 40% of the LNZ101 treatment subjects have at least a 3-line (15-letter) improvement from the pre-dose measurement of monocular BCDVA while the vehicle treatment has 7.5% of subjects with a 3-line improvement, assuming the non-responder concordance is at least 52.5%. With the same assumption on the vehicle treatment response rate (7.5%), this sample size will still provide ≥ 76% power to detect a significant treatment difference if only 32% of subjects in the LNZ101 treatment have at least a 3-line improvement, assuming non-responder concordance is at least 60.5%. [redacted] Assuming the LNZ101 treatment maintains a response rate of 22%, this sample size will provide ≥ 20% power to detect a significant treatment difference at 7 hours or later, assuming non-responder concordance is at least 66%.

6. Data Preparation

6.1 Input Data

Study data will primarily be recorded on the electronic case report forms (eCRFs) supplied by SDC using iMEDNET EDC (electronic data capture) system.

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

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

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

6.2 Output Data

Data from 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.

SDTM will follow the SDTM version 1.4 model and will be implemented using the SDTM Implementation Guide version 3.3 and the SDTM Controlled Terminology version 2022-03-25. ADaM data will follow the ADaM version 2.1 model and will be implemented using the ADaM Implementation Guide version 1.3. Both SDTM and ADaM will be validated using Pinnacle 21 version 2.2. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model.

7. Analysis Populations

7.1 Modified Intent-to-Treat

The mITT Population consists of subjects with study eye baseline/pre-treatment monocular BCDVA at 40 cm ≥ 0.42 logMAR and a non-missing monocular BCDVA at 40 cm at 1 hour-post dose at each visit. Pairwise comparisons between treatments and changes from pre-treatment will use the mITT Population. Because inclusion in the mITT is assessed at each treatment visit separately it is possible subjects are included at some visits/treatments but not at others. All data will be included and no subjects will be excluded because of protocol violations/deviations.

7.2 Intent-to-Treat

The Intent-to-Treat (ITT) population consists of the study eye with Visit 1 baseline monocular BCDVA at 40 cm meeting the logMAR requirements listed in inclusion criteria in Section 5.3 of the protocol. All data will be included and no subjects will be excluded because of protocol violations/deviations. The ITT population will be analyzed as randomized and will be used for the sensitivity analyses on the primary and secondary monocular efficacy endpoints.

7.3 Per Protocol

The Per Protocol (PP) population is a subset of the ITT population and includes subjects with no major protocol violations/deviations likely to affect the primary efficacy endpoint. This population will be analyzed as treated for confirmatory and sensitivity analyses.

7.4 Safety

The Safety population includes all randomized subjects who receive at least one dose of study medication. The Safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

8. General Statistical Considerations

8.1 Unit of Analysis

The unit of analysis in this study will be the study eye for all efficacy and safety summaries. The study eye is defined as below.

Dynamic Study Eye: One eye per subject will be designated as the study eye at each visit. The Dynamic Study Eye is the eye at each visit with the highest logMAR score for baseline monocular BCDVA at 40 cm. If both eyes have the same BCDVA at 40 cm, the study eye will be selected as the eye with the least hyperopic sphere (i.e., most negative value if both are negative, smallest positive value if both are positive, negative value if one is positive and one is negative) determined by manifest refraction within 3 months of Visit 1 or at Visit 1. If both eyes have equal sphere, the right eye will be selected as the study eye.

Additionally, non-ocular adverse events (AE) and medical history will be presented at the subject level.

The non-study eye will be referred to as the fellow eye. Non-study eye safety summaries will also be presented as appropriate.

8.2 Missing or Inconclusive Data Handling

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

As this is a crossover study, every subject will receive a different treatment at Visits [redacted] For all safety and efficacy analysis, baseline refers to the assessment done prior to treatment administration at each visit or if there are multiple pre-dose assessments, it is the last measurement prior to the first dose of study medication. Change from baseline will be calculated as follow-up visit/time point – baseline.

[redacted]

[redacted]

8.5 Data Analysis Conventions

All data analysis will be performed by Statistics & Data Corporation (SDC). Statistical programming and analyses will be performed using SAS® version 9.4 or higher. Output will be provided in rich text format (RTF) for tables, and portable document format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, randomized sequence, visit (as applicable), and treatment based on all randomized subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between active treatments and placebo will be calculated as active minus placebo and change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests will be two-sided with a significance level of 0.10 ($\alpha = 0.10$) unless otherwise specified. Confidence intervals (CI) for differences between treatments will be two-sided at 90% confidence. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

Unless otherwise specified, summaries will be presented by treatment and, where appropriate, visit.

8.6 Adjustments for Multiplicity

There will be no adjustments for multiplicity in testing the primary efficacy endpoint at each time point at a distance of 40 cm in this proof of concept study. There will be also be no adjustments for multiplicity for multiple treatments and multiple comparisons to vehicle.

9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the study, and discontinued from the study. Disposition will be summarized by treatment sequence for all randomized subjects.

The number of subjects in ITT, PP and Safety analysis populations will be displayed by treatment sequence. Percentages of number of subjects will be calculated using randomized subjects as the denominator. Since inclusion to the mITT Population is assessed at each visit separately, the number and percentage of subjects in mITT Population at each visit will be presented by eye, treatment [redacted]. A subject listing of inclusion in each of these populations will be presented.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment sequence for all randomized subjects. The reasons for study discontinuation that will be summarized include AE, lost to follow-up, physician decision, protocol violation, sponsor termination of study, withdrawal by subject, and, other. Discontinuations due to COVID-19 will also be displayed. A subject listing will be provided which includes the date and reason for premature study discontinuation.

The number and percentage of subjects with major protocol deviations will be summarized by treatment and overall, for all randomized subjects. Protocol deviations will be classified as major or minor prior to the closure of the database during a masked review of each protocol deviation.
A subject listing will be provided which includes the date of the deviation, the deviation description, the classification of whether the deviation was judged to be major or minor, and whether the deviation was COVID-19 related or not.

In addition, subject listings will include randomization/treatment sequence (actual vs assigned), informed consent date and exclusions from the PP population.

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

The demographic variables collected in this study include age, sex, if female, child-bearing potential, race, ethnicity, and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Iris color will be presented at the subject level with a category for heterochromia. Sex, race, ethnicity, and iris color will be presented using descriptive summary statistics with counts and percentages. Age (years) will be summarized, overall and by treatment sequence, using continuous descriptive statistics. Age will be reported in years and calculated using the following formula:

Age = (informed consent date – date of birth) / 365.25, truncated as an integer

Demographic variables will be summarized for the ITT, Safety and Per-Protocol populations by treatment sequence and overall, in tables. A subject listing that includes all demographic variables will be provided.

10.2 Pretreatment Variables

Pretreatment variables are measured to ensure the safety and eligibility of subjects at Visit 1. Subject level listings of the assessments below will be used to present pretreatment information from the ITT population at the eye level when appropriate.

[redacted]

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment sequence at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the ITT and Safety Populations. Ocular medical history will be similarly summarized at the subject level. 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.

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

11.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary Version Enhanced B3, March 2022 and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then the next lowest 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. Any uncoded terms will be summarized under the ATC classification and preferred name of “Uncoded.”

Concomitant medications for each treatment are defined as those that are in use during dosing or started after dosing but ended before the next treatment in the sequence or study completion/discontinuation..

Concomitant medications will be summarized using the ITT population. Medications will be tabulated for each treatment 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. Percentages will be based on the number of subjects in each treatment. Tables and listings of concomitant medications will be generated separately for ocular and non-ocular data.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

The study drug will be administered by a trained study technician; therefore, dosing compliance and exposure cannot be calculated. Treatment administration will be listed by subject.

13. Efficacy Analyses

13.1 Primary Analysis

The primary efficacy variable in this study is the percentage of subjects with at least a 3-line (15-letter) improvement from the pre-dose measurement of [redacted] monocular BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4 m) [redacted]. Primary analysis will use the population as described in Section 7.1. The primary analyses will separately compare the LNZ101 treatment versus the vehicle treatment, and the LNZ100 treatment versus the vehicle treatment. [redacted]

Counts and percentages of subjects who meet the primary efficacy criteria described above will be presented by treatment and eye. Inferential testing of the percentage of subjects, who meet the primary efficacy criteria above, will be done by generating an odds ratio (along with 80% and 90% CIs and p-value) from a logistic model (binomial error and logit link) estimated by generalized estimating equation methods. This model accounts for the correlations between treatments and periods within a subject. Aspects of the model include:

- Response Measure: Indicator of whether the subject had at least a 3-line (15-letter) improvement [redacted] from pre-dose in the monocular assessment of BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4 m).
- Fixed effect explanatory measures: sequence, period, and treatment.
- Repeated measures correlation will be estimated with an unstructured variance-covariance matrix in the GEE model. If the model fails to converge, alternative covariance structures, such as AR(1), Toeplitz, or compound symmetry, will be tried in the order specified.

Example SAS code is shown here:

```
proc genmod data=final descending;
      class subjid trtseqan avisitn trtan;
      model aval = trtseqan avisitn trtan/ type3 wald corrb dist=binomial
            link=logit alpha=.1;
      repeated subject=subjid/type=un  corrw;
      lsmeans trtan/ oddsratio pdiff cl alpha=.1;

run;
```

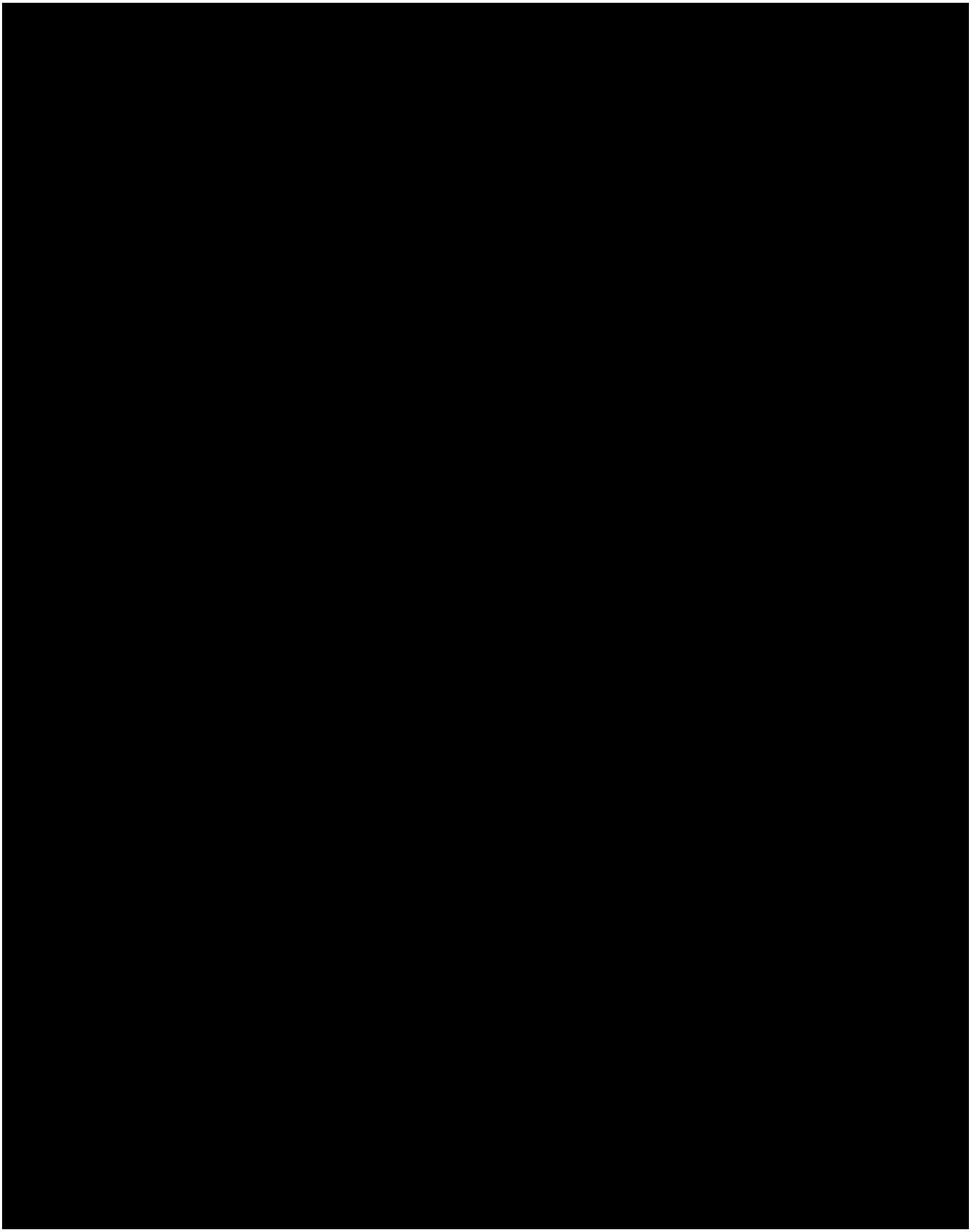
- *DESCENDING* = option that specifies that 1 is a yes and 0 is a no (NOTE: SAS default is ascending)
- *ALPHA* = option specifies the family-wise error rate, default is .05. (NOTE: code will be run with both .05 and .1 for confidence interval output)
- TRTSEQAN = treatment sequence
- AVISITN = visit number (Visits 2, 3, and 4)
- TRTAN= treatment / study drug

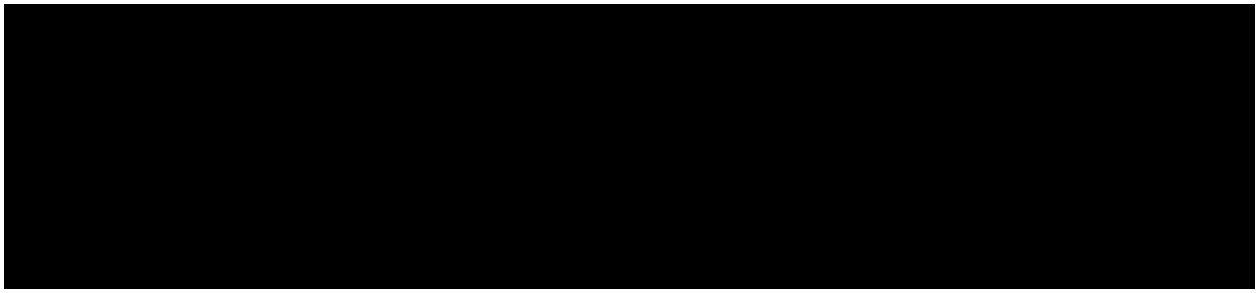
- `AVAL` = indicator for the efficacy variable, (≥ 3-line improvement in BCDVA at 40 cm and no loss in BCDVA at ≥ 5 letters at 4 m = 1 or < 3-line improvement in BCDVA at 40 cm and no loss in BCDVA at ≥ 5 letters at 4 m = 0)
- `BINOMIAL` = the error term as a binomial distribution with a logit link (Note: SAS default is *link* = `LOGIT` when `DIST=BIN`)

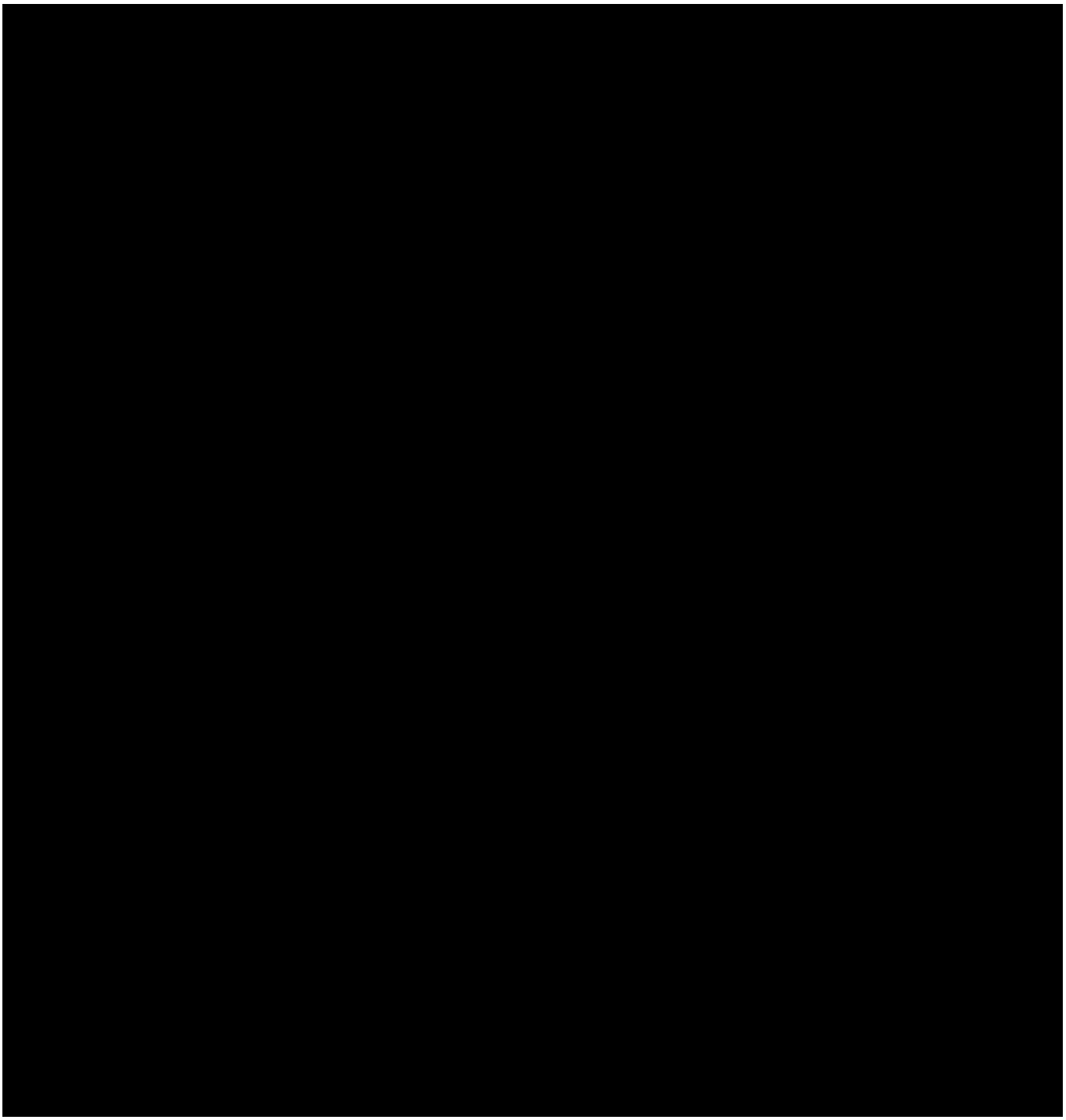
The proportion of subjects meeting the primary efficacy criteria in each treatment and eye will also be analyzed using the McNemar's test. This tests for marginal homogeneity and the p-value for this test will be reported. An example of McNemar's test in SAS is:

```
PROC FREQ DATA=<DATA> (WHERE=(<SELECTION CRITERIA>));
   WEIGHT COUNT;
   TABLES TRTAN_1*TRTAN_2 / AGREE;
   EXACT MCNEM;
RUN;
```

Note that the *WHERE* statement *<SELECTION CRITERIA>* will need to include pairs of treatments (TRTAN_1, TRTAN_2) with counts of responders and non-responders. The primary endpoint will also be analyzed on the ITT and PP populations.







15. Safety Analyses

All safety analyses will be conducted using the Safety population.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the first dose of study drug, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE. The AE reporting period ends upon study exit. Study drug includes the investigational drug under evaluation and vehicle given during any stage of the study. All AEs will be coded using MedDRA version 25.0.

Treatment-emergent adverse events (TEAE) are defined as any event that occurs or worsens on or after the first dose of study drug instillation. TEAE for a treatment is defined as an AE that started or worsened on or after that specific treatment administration and before the administration of subsequent treatment or study completion/discontinuation.. Adverse events recorded in the eCRF which began prior to the first treatment 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 him/her 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 is 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.

The expectedness of an AE is determined based upon existing safety information about the investigational product using these explanations:

- Unexpected: an AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- Expected: an AE that is listed in the IB at the specificity and severity that has been observed.
- Not applicable: an AE unrelated to the investigational product.

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 and overall subjects. This summary will also include breakdowns of TEAEs further categorized as ocular (study eye and fellow eye separately) or non-ocular, treatment-related TEAEs, Treatment-Emergent serious AEs (SAEs), TEAEs leading to early treatment discontinuation, TEAEs leading to death, and TEAEs (ocular and non-ocular) by maximum severity.

The following summaries will be presented by treatment, 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 will be listed in alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

- Ocular TEAEs
- Non-ocular TEAEs
- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs.
- Expected TEAEs
- Unexpected TEAEs
- Treatment-Emergent SAEs

Summaries of TEAEs by maximum severity will be presented for ocular AEs and non-ocular AEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within

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

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

15.2 Best-Corrected Distance Visual Acuity at 40 cm in Letter Score

The observed and change from baseline in monocular and binocular BCDVA letter score at 40 cm at every scheduled visit at all post-treatment time points [redacted] will be summarized in tables by treatment and eye using the Safety population.

15.3 Low-Luminance Best-Corrected Distance Visual Acuity

Monocular and binocular low-luminance BCDVA using an ETDRS chart calibrated for testing at 4 meters is conducted [redacted] Results will be recorded in logMAR units.

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

15.4 Slit Lamp Biomicroscopy Examination and Dilated Fundoscopy

A slit lamp biomicroscopy examination will be conducted on both eyes at all scheduled visits and at the last time point for each visit in the eyelid, conjunctiva, cornea, anterior chamber, iris, and lens. The results will be graded as normal, not clinically significant (NCS), or clinically significant (CS).

A table will summarize results using counts and percentages for each treatment at each time point and location for each eye. Percentages will be based on the number of subjects in each treatment with responses. Shift tables and subject level listings will also be provided.

Dilated fundoscopy will be done at Visit 1 and the results will be provided in a listing.

15.5 Conjunctival Hyperemia

Conjunctival hyperemia is measured [redacted] Conjunctival redness will be summarized by treatment, for the study and fellow eye separately, using continuous descriptive summary statistics in a table. Change from baseline will also be calculated and summarized using descriptive summary statistics in a table. The data for conjunctival redness will be presented in a listing.

15.6 Intraocular Pressure

Intraocular pressure is measured [redacted] Observed IOP values will be summarized by treatment 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.

15.7 Urine Pregnancy Test

Female subjects of childbearing potential will have a urine pregnancy test at the site at each visit. A subject level listing by visit will be produced.

16. Other Analyses

16.1 Patient Reported Outcome Questionnaire

Subjects will be required to answer Patient Reported Outcome (PRO) questionnaire[redacted]. Counts and proportions for the responses to the following questions will be presented by treatment on the mITT and Safety Population.

[redacted]

16.2 Monocular and Binocular Uncorrected Distance Visual Acuity

Monocular and Binocular uncorrected distance VA at 4 m will be collected a[redacted]. The observed and change from baseline logMAR values from these assessments will be summarized in tables by treatment and eye using the safety population. A subject listing of Monocular and Binocular uncorrected distance VA will also be produced.

16.3 Drop Instillation Assessment

[redacted]

17. Changes from Protocol-Stated Analyses

None.

18. References

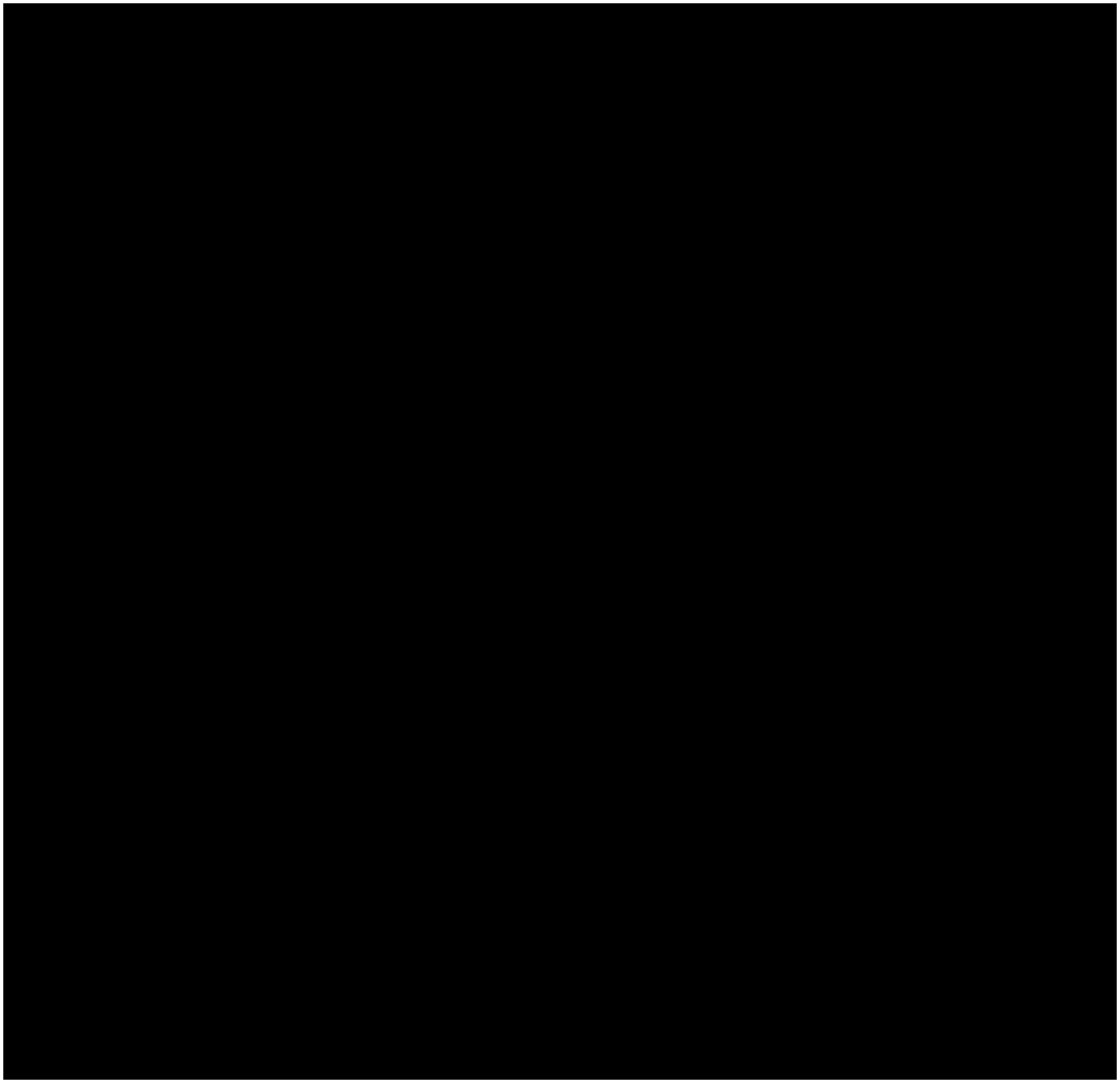
- Lenz Protocol 21-100-0007 Version 4.0

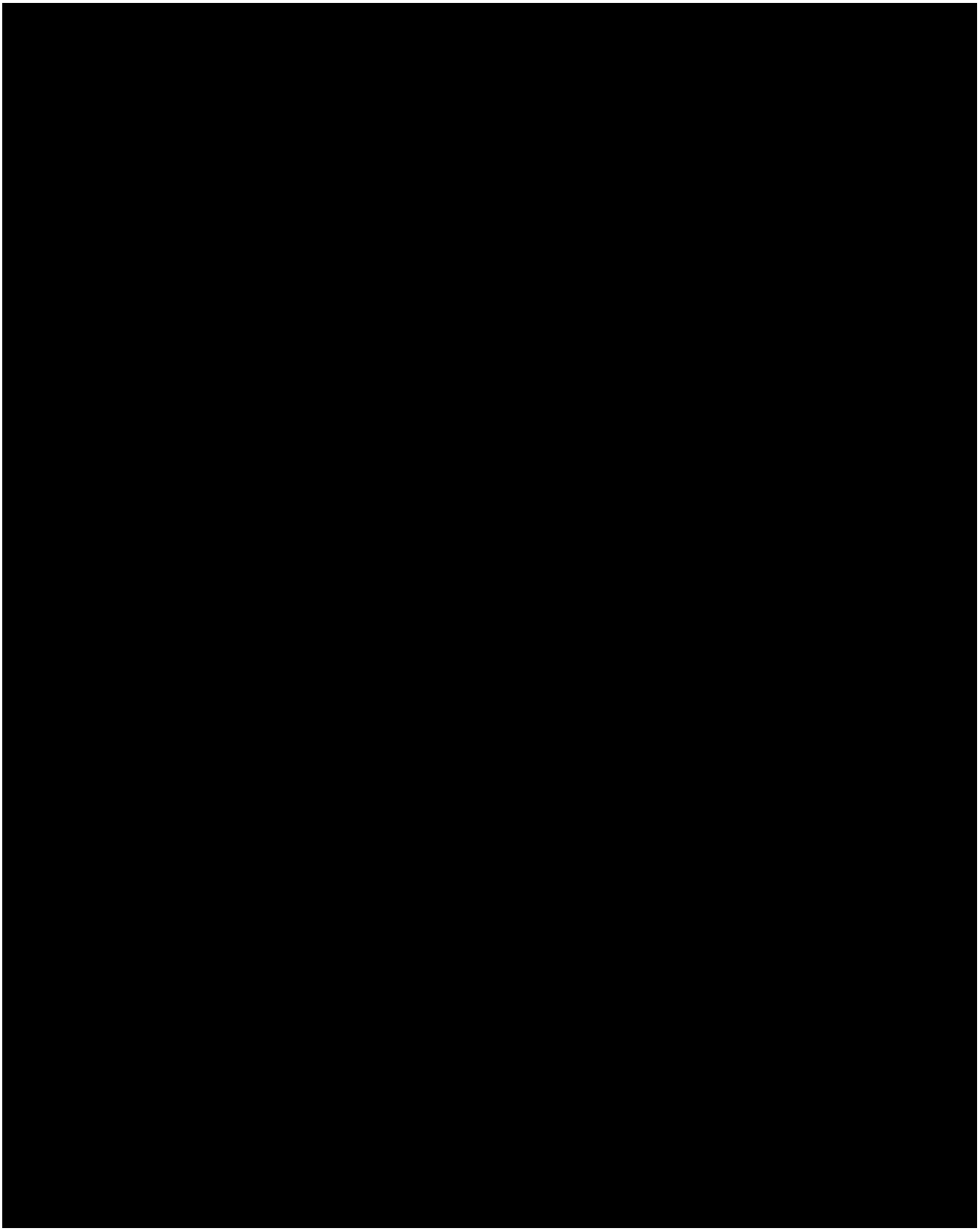
19. Revision History

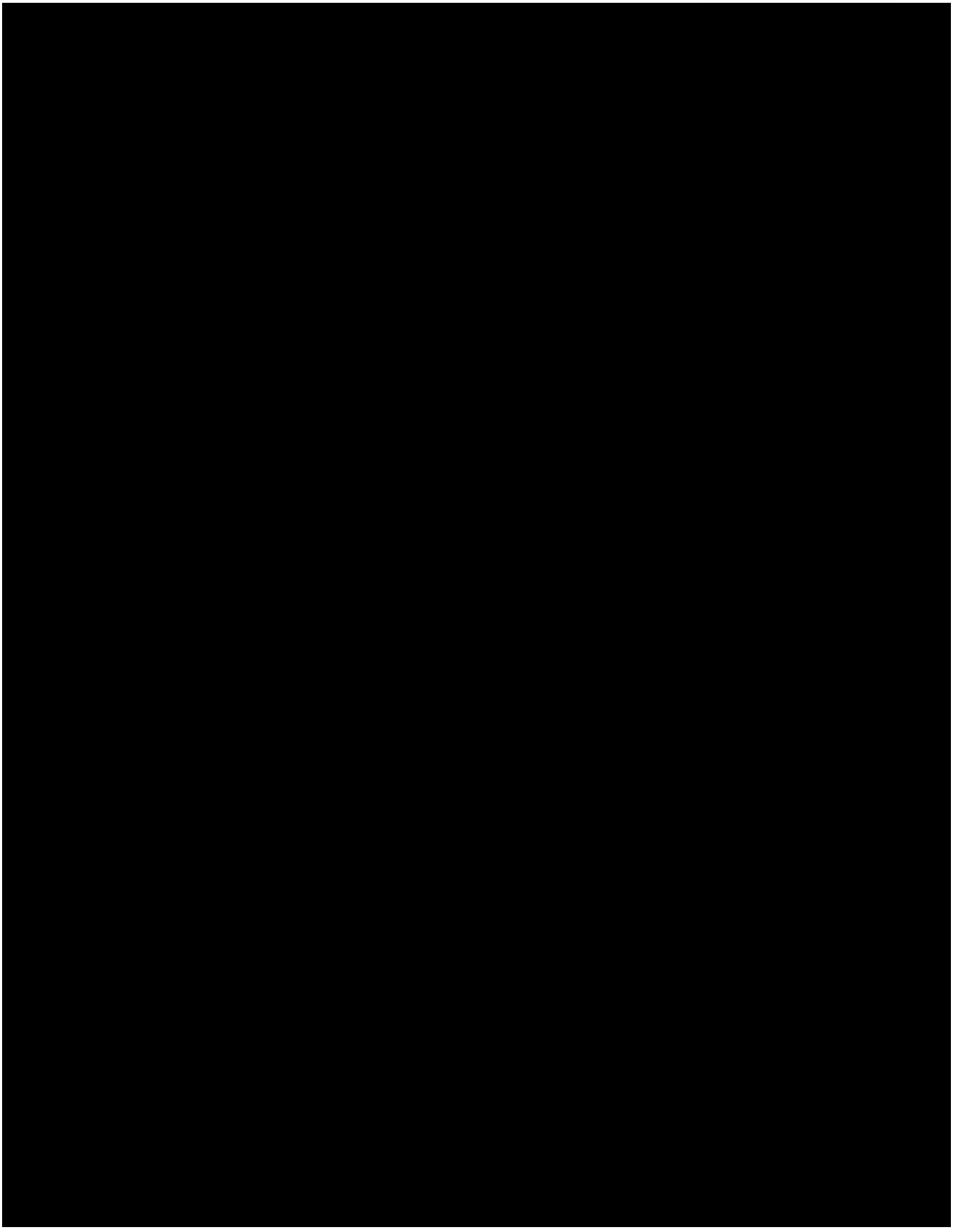
Documentation of revision to the SAP will commence after approval of the final version 1.0.

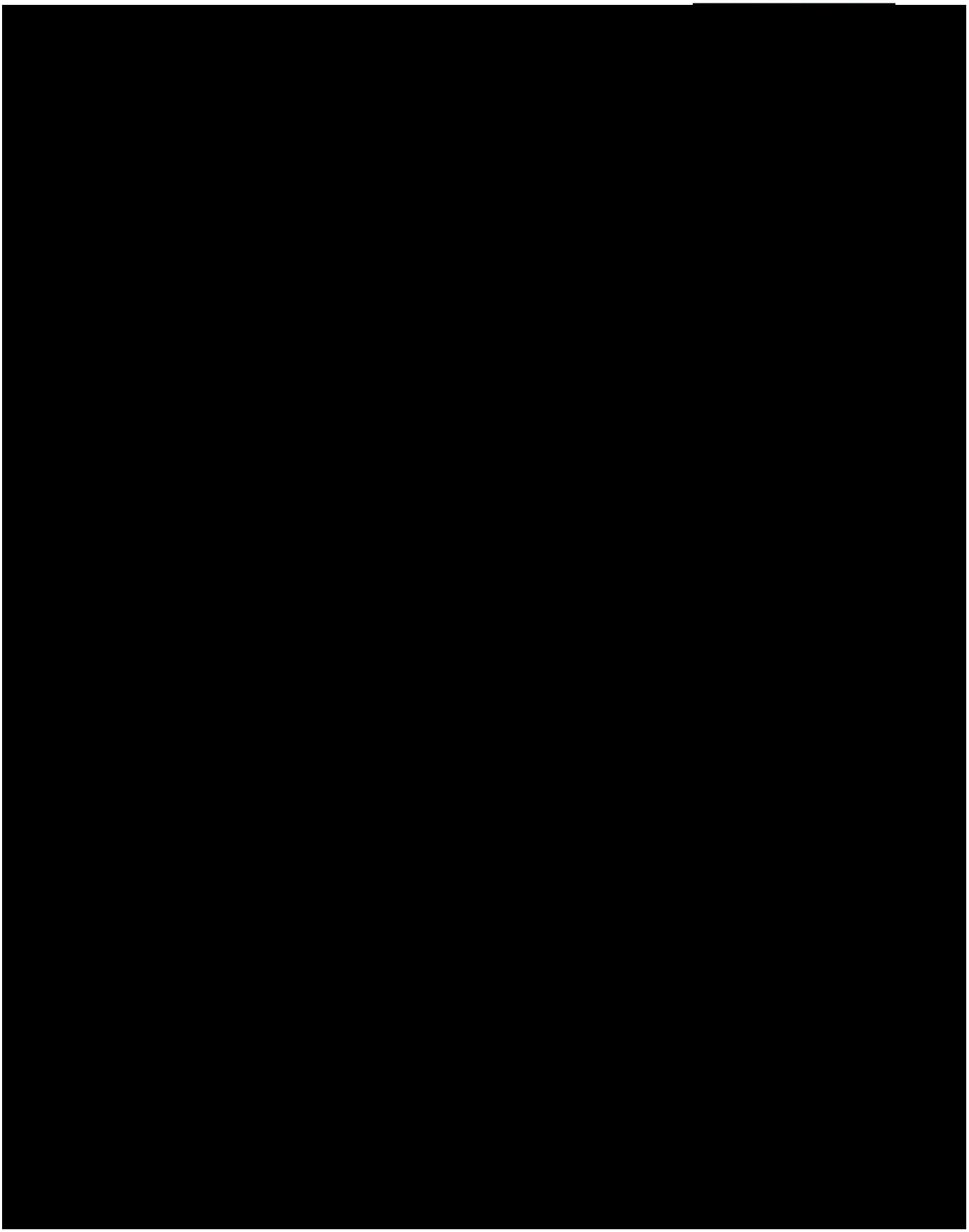
20. Tables

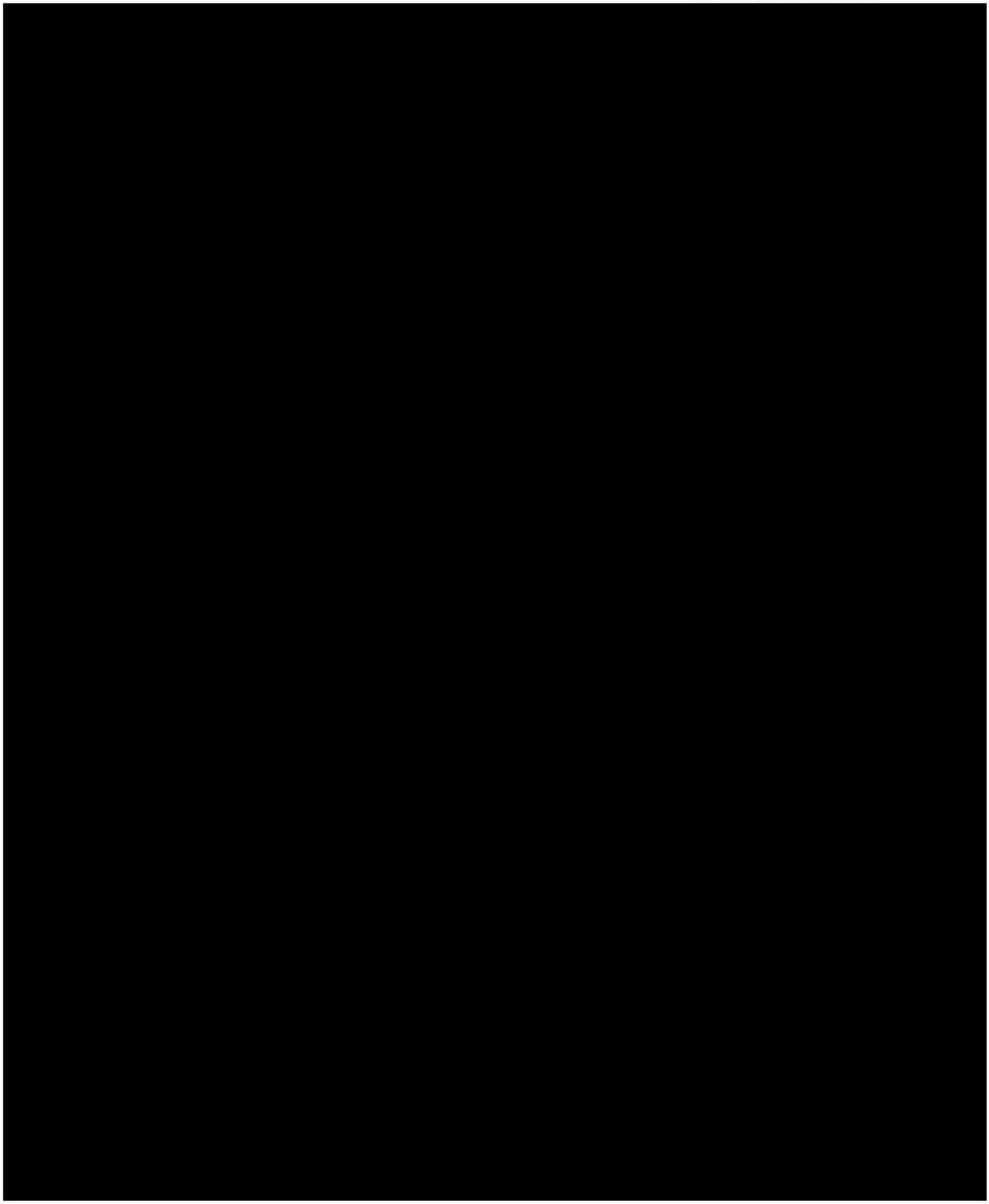
Tables that will be included in the topline delivery are shown in boldface font.

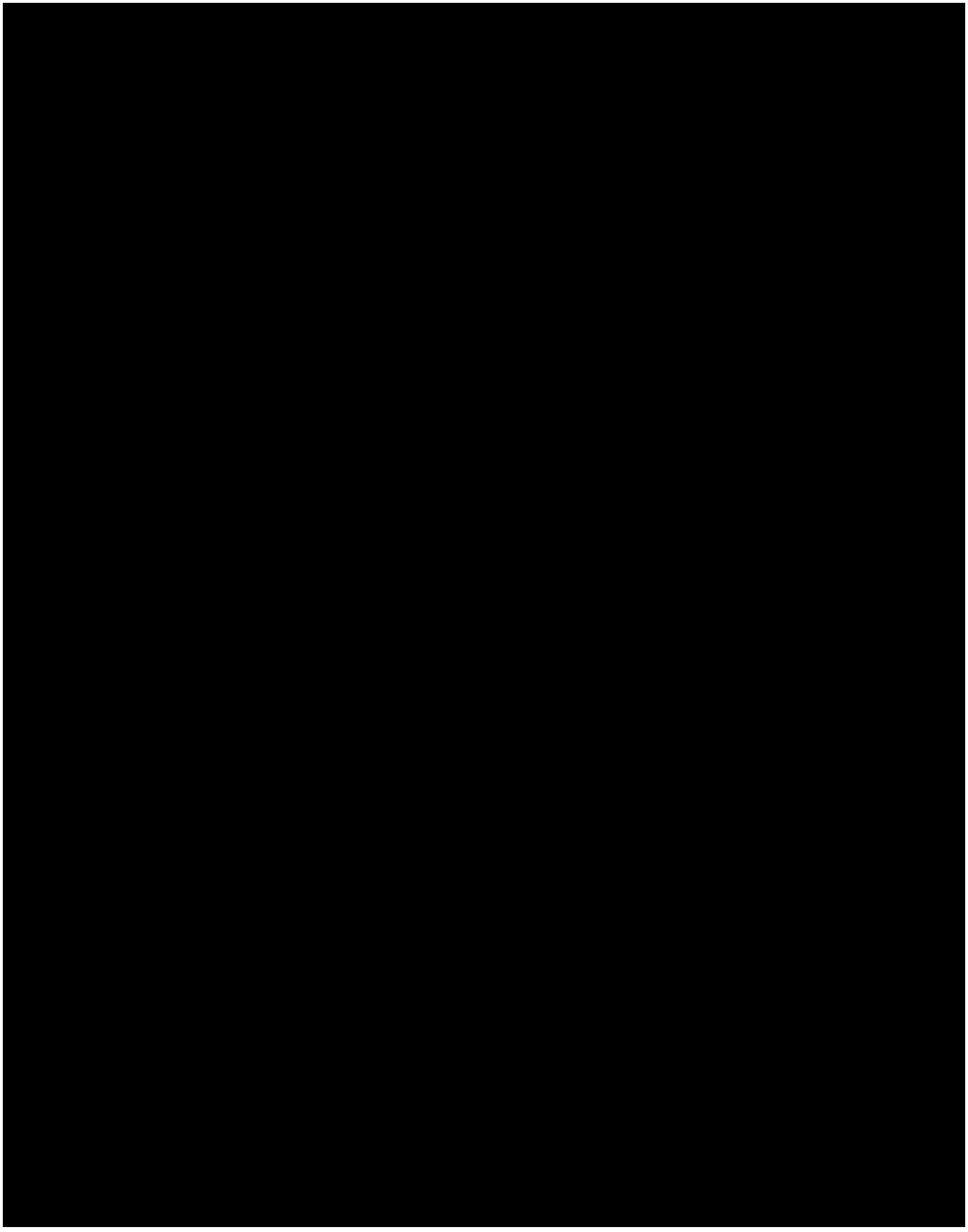


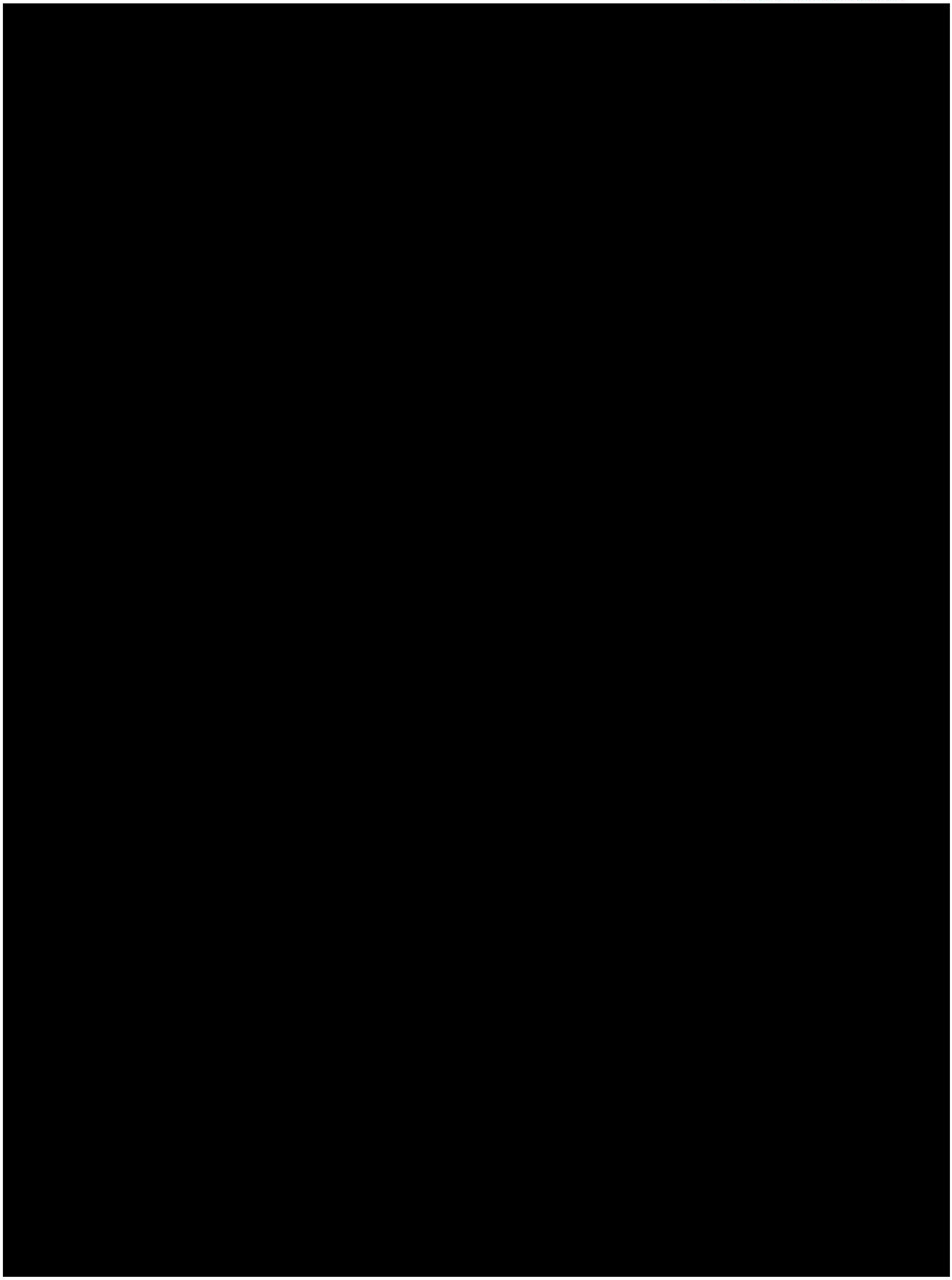


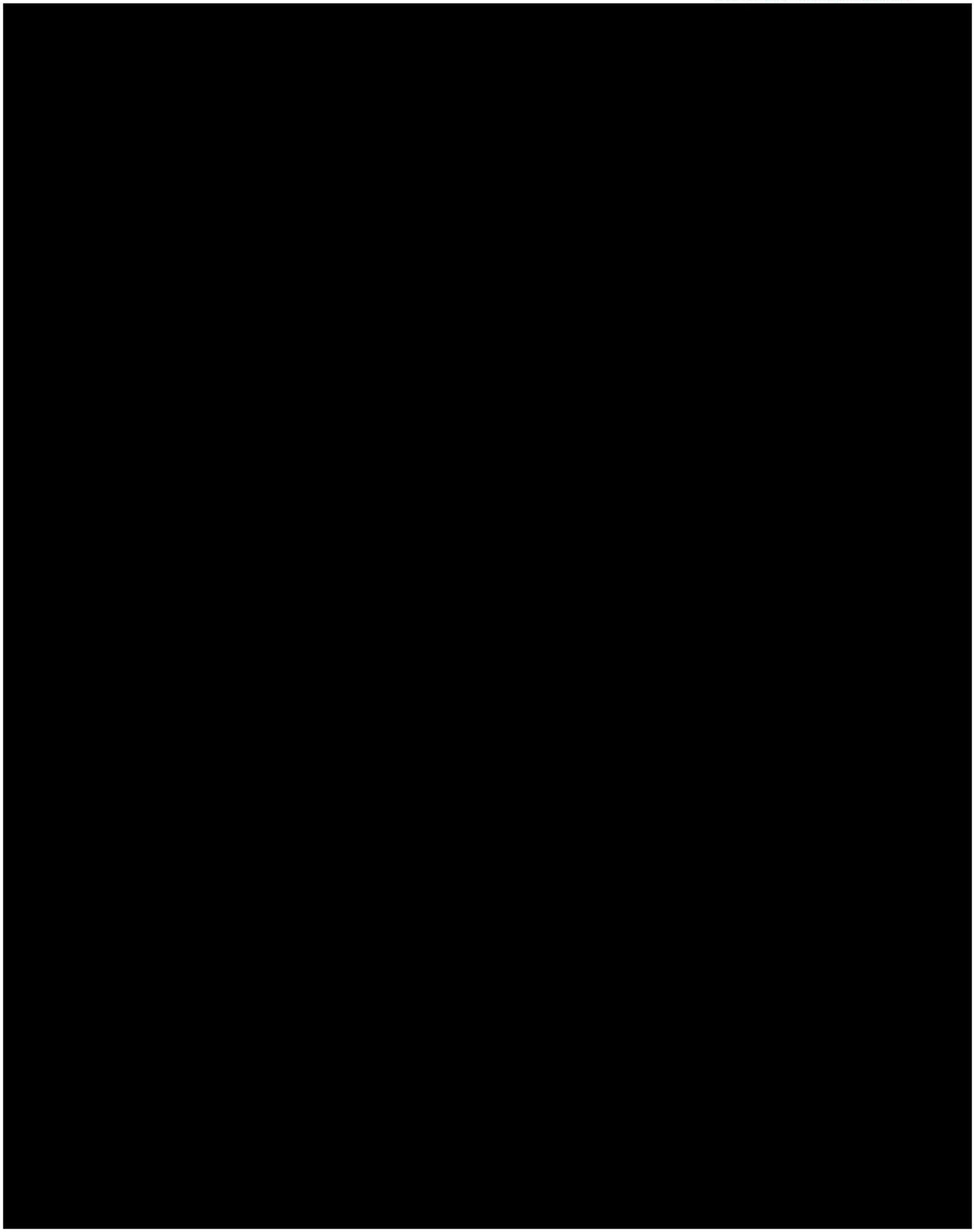












[redacted]