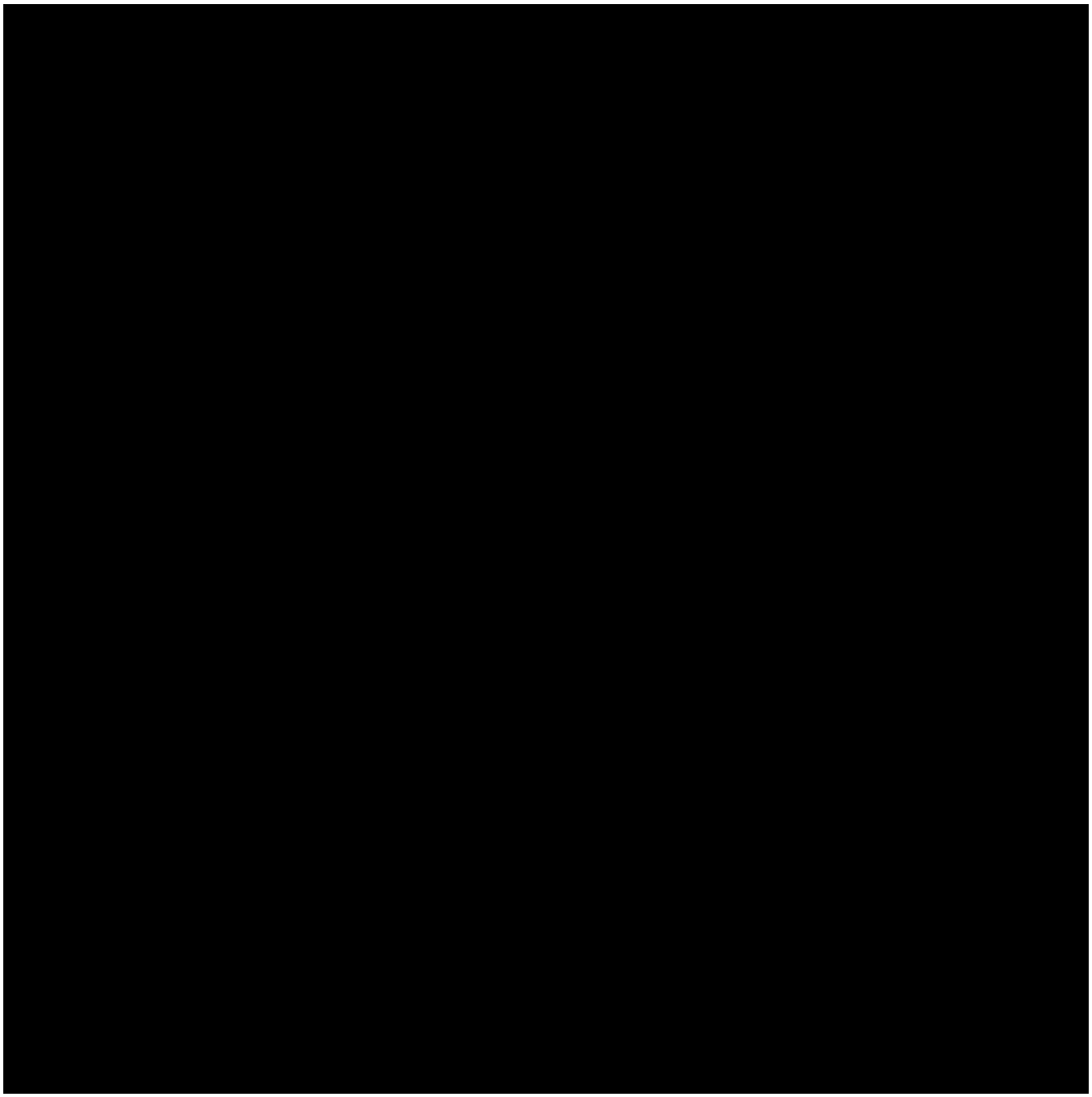
Clinical Trial Protocol 22-150-0018

Protocol Title:	A Multi-Center, Double-Masked Phase 3 Evaluation of the Safety and Efficacy of LNZ101 for the Treatment of Presbyopia
Protocol Number:	22-150-0018
Study Phase:	Phase 3
Investigational Product Name:	LNZ101 [redacted] Ophthalmic Solution LNZ100 [redacted] Ophthalmic Solution
IND/IDE/PMA Number:	120,609
Indication:	Presbyopia
Investigators:	TBD
Sponsor:	LENZ Therapeutics, Inc. [redacted]
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
IRB/IEC:	Alpha IRB 1001 Avenida Pico, Suite C, #497 San Clemente, CA 92673 949-542-3882 www.alphairb.com

	Date
Original Protocol:	Version 1.0 (17 Nov 2022)
Amendment 1	Version 2.0 (30 Jan 2023)
Amendment 2	Version 3.0 (02 May 2023)
Amendment 3	Version 4.0 (16 Jun 2023)
Amendment 4	Version 5.0 (31 Jul 2023)

Confidentiality Statement



1.0 SYNOPSIS

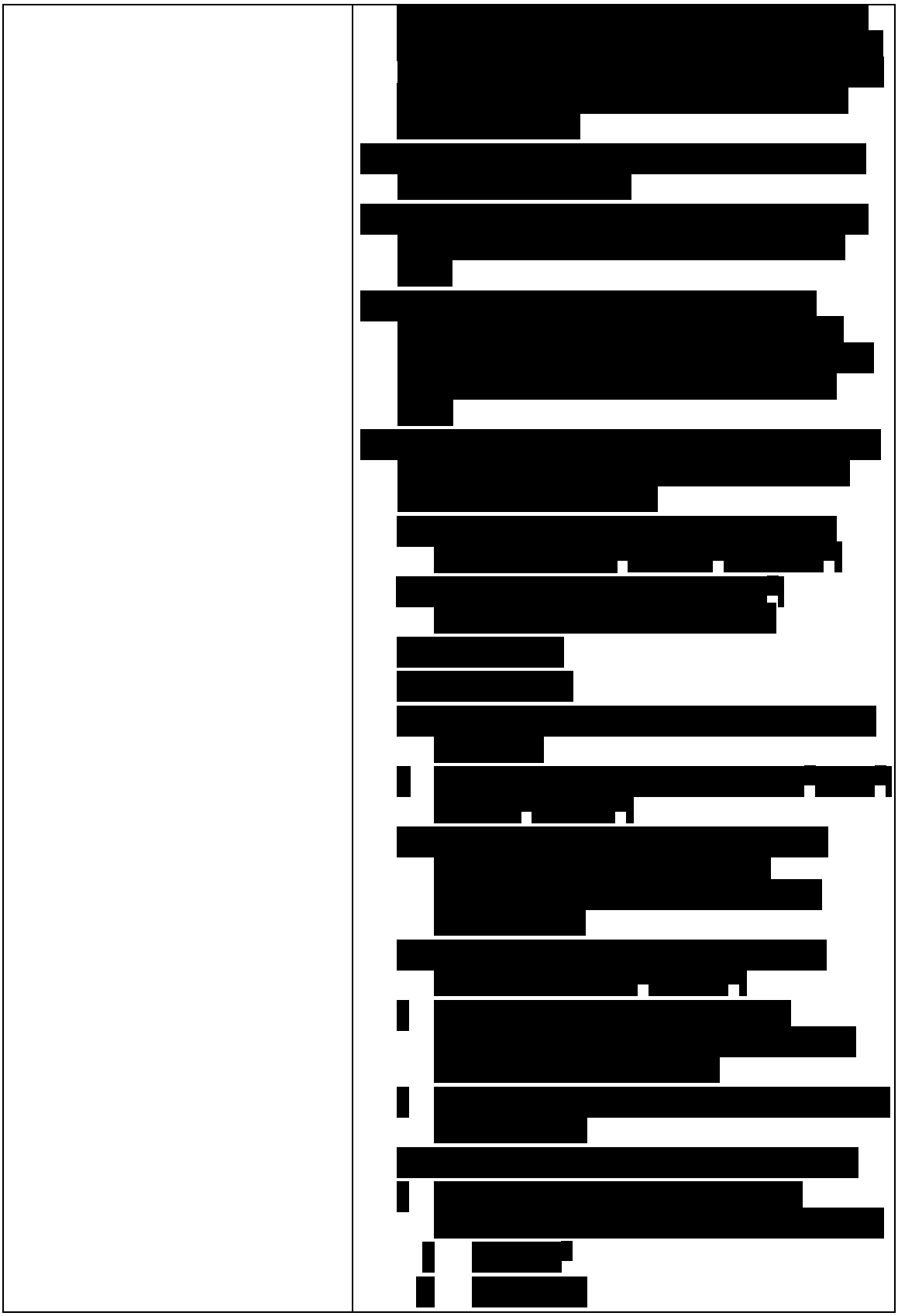
Protocol Title:	A Multi-Center, Double-Masked Phase 3 Evaluation of the Safety and Efficacy of LNZ101 for the Treatment of Presbyopia
Protocol Number:	22-150-0018
Investigational Products:	LNZ101 [redacted] ophthalmic solution LNZ100 [redacted] ophthalmic solution Vehicle ophthalmic solution
Study Phase:	Phase 3
Primary Objective:	To evaluate the safety and efficacy of LNZ101/LNZ100 compared with vehicle for the treatment of Presbyopia.
Secondary Objective:	Not applicable
Overall Study Design:	
Structure:	A multi-center, double-masked, randomized, vehicle-controlled, safety and efficacy study
Duration:	Approximately 6 weeks
Controls:	**Screening Control:** [redacted] **Randomized Control Treatment:** Vehicle ophthalmic solution
Dosage/Dose Regimen/ Instillation/Application/Use:	Enrolled subjects will be randomized to receive LNZ101, LNZ100, or vehicle [redacted]. Subjects will dose for 6 weeks.
Summary of Visit Schedule:	• Visit 1 (Day -60 to -4): Screening; • Visit 2 (Day 1): [redacted]

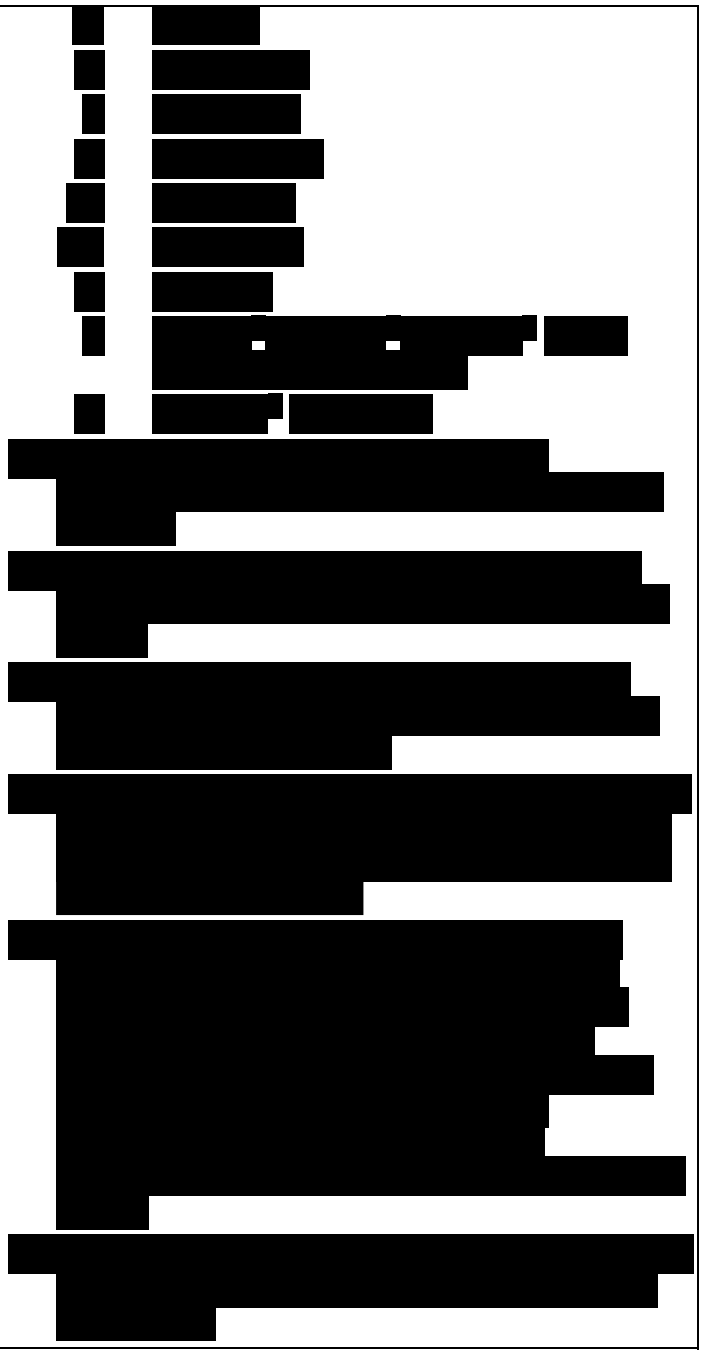
	• [redacted]
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to treatment and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints. [redacted]
Number of Subjects:	Approximately 222 subjects will be enrolled at Visit 2. [redacted]
Condition/Disease:	Healthy adult subjects ages 45 to 75 years who have presbyopia
Inclusion Criteria:	Subjects must: 1. Be able and willing to provide written informed consent and sign a Health Information Portability and Accountability Act (HIPAA) form prior to any study procedure being performed; 2. Be able and willing to follow all instructions and attend all study visits; 3. Be 45-75 years of age of either sex and any race or ethnicity at Visit 1; [redacted]

	[redacted]
Exclusion Criteria:	1. Subject must not be a female of childbearing potential who is currently pregnant, nursing, or planning a pregnancy; 2. Subject must not have known contraindications or sensitivity to the use of any of the study medications or their components; 3. Neither eye can have an active ocular infection at Visit 1 or at Visit 2 (bacterial, viral, or fungal), positive history of an ocular herpetic infection, preauricular lymphadenopathy, or ongoing, active ocular inflammation (e.g., moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis); 4. Neither eye can have moderate or severe dry eye [redacted]

[1] Punctal plugs are acceptable if they have been in place for a minimum of 90 days prior to visit 1.

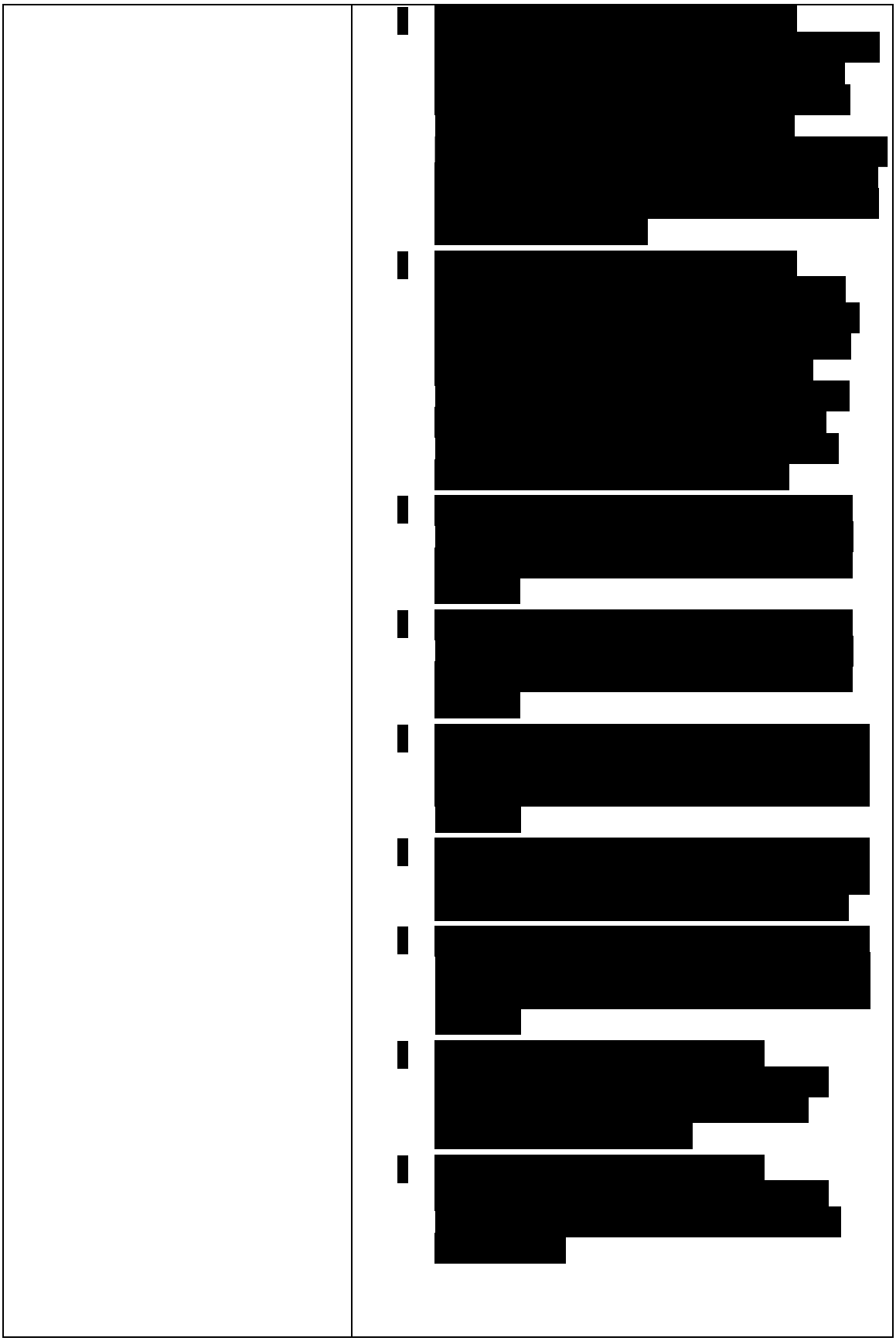
	5. Neither eye can have clinically significant abnormal lens findings (e.g., cataract) including early lens changes and/or any evidence of a media opacity during dilated slit-lamp biomicroscopy and fundus exam documented within 3 months of Visit 1 or at Visit 1; [redacted]



	
Study Formulations:	LNZ101 ophthalmic solution LNZ100 ophthalmic solution Brimonidine ophthalmic solution
Evaluation Criteria:	

[2] Any blood sugar in an otherwise normal, non fasting blood chemistry panel that is greater than 150mg/dl would be considered abnormal and indicative of a diabetic or prediabetic state and is exclusionary.

Efficacy Measures and Endpoints:	**Primary Efficacy Endpoint:** • Percentage of subjects who 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]
Safety Measures:	• Adverse events (AE) (reported, elicited, and observed) • Pregnancy test [redacted] • Monocular and binocular BCDVA (normal and low-luminance) • Slit lamp biomicroscopy • IOP • Dilated fundus exam [redacted] • Conjunctival redness
Other:	• Dark Adapted Pupillometry • Patient-reported outcome (PRO) questionnaire • Drop instillation assessment

General Statistical Methods and Types of Analyses Analysis Sets:

Full Analysis Set (FAS) – The 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.

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

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.

Unit of Analysis:

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

[redacted]

General Considerations:

In general, quantitative/continuous data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum). Qualitative/categorical data will be summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level.

For all variables, baseline is defined as the last measurement taken prior to the administration of first dose of study drug at Visit 2. Change from baseline will be calculated as follow-up measure minus baseline measure.

[redacted]

[redacted]

Sample Size

A sample size of 222 subjects (74 per arm) yields >99% power to establish superiority of LNZ101/LNZ100 to vehicle in the proportion of study eyes demonstrating a ≥ 3-line (15-letter) improvement or greater from baseline in BCDVA at 40 cm and no loss in BDVA ≥ 1 line (5 letters) at 4 [redacted]

Primary Efficacy Analyses

The primary efficacy endpoint in this study is the percentage of study eyes with a ≥ 3-line (15-letter) improvement in BCDVA at 40 cm from baseline and no loss in best distance corrected visual acuity ≥ 1 line (5-letter) at 4 m [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% confidence intervals (CIs) and p-values will be presented.

Treatment comparison will also be made using Pearson's chi-squared test or Fisher's exact test if any of the expected cell counts are less than five as a sensitivity analysis to the primary model above.

[redacted]

Safety Analysis

All safety data will be analyzed using the Safety set. Safety of LNZ101 and LNZ100 will be assessed by the review of all safety parameters.

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms and be presented in a data listing. Treatment emergent AEs (TEAEs), those that occur after the first dose of study drug, will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Similar summaries will also be presented for expected and unexpected TEAEs, treatment emergent SAEs, TEAEs related to the study drug, and TEAEs by severity. When reporting the incidence of AEs, a subject will only be counted once if they ever experience an event within the SOC and ever experience the individual PT within each treatment group. Ocular and non-ocular events will be summarized separately.

Actual results and changes from baseline results in monocular and binocular BCDVA (normal and low-luminance), slit lamp biomicroscopy, IOP, dilated fundus examination, and conjunctival redness will be summarized descriptively at each visit by treatment group.

Full details of the safety analyses will be specified in the formal SAP.

Summary of Known and Potential Risks and Benefits to Human Subjects

Approved pharmacologic treatment for presbyopia is limited. Pilocarpine ophthalmic solution 1.25% is the only approved pharmacologic treatment for presbyopia in adults to date. There are currently no marketed Aceclidine-Brimonidine combination products. A 2% concentration of Aceclidine was approved in several European countries in 1969 for the treatment of glaucoma, and Aceclidine has been used in humans at concentrations of up to 4%. Possible AEs associated with Aceclidine include redness or brow ache (Romano 1970, Randazzo et al. 2005). Fewer adverse effects have been reported with Aceclidine (no angle closure, fewer subjects reporting pain on instillation, greater comfort with long-term use, and no tachyphylaxis) compared to other miotics, like pilocarpine (Francois and Goes 1977; Romano 1970).

Brimonidine was approved in the U.S. for human use in 1996 for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. It is commercially available in the U.S. at up to 0.2% concentration. Dosing at this concentration has been shown to be generally safe and effective. Adverse ocular effects of Brimonidine include possible discomfort, irritation, blurred vision, and light sensitivity.

In addition, vitreous floaters have also been reported.

The concentrations proposed for use in this study [redacted] are substantially lower than the concentrations in common clinical use for both of these active ingredients.

TABLE OF CONTENTS

1.0 SYNOPSIS 3
TABLE OF CONTENTS 18
LIST OF ABBREVIATIONS 21
2.0 INTRODUCTION 23
3.0 STUDY OBJECTIVES 23
3.1 Primary Objective 23
4.0 CLINICAL HYPOTHESES 23
5.0 OVERALL STUDY DESIGN 24
6.0 STUDY POPULATION 24
6.1 Inclusion Criteria 24
6.2 Exclusion Criteria 25
6.3 Cohort Assignment 28
6.4 Withdrawal Criteria 28
7.0 STUDY PARAMETERS 29
7.1 Efficacy Endpoints Primary Efficacy Endpoint: 29
7.2 Safety Endpoints 32
8.0 STUDY MATERIALS 33
8.1 Study Treatments 33
8.1.1 Investigational Product 33
8.1.2 Instructions for Use and Administration 33
[redacted]
9.0 STUDY METHODS AND PROCEDURES 34
9.1 Subject Entry Procedures 34
9.1.1 Overview 34
9.1.2 Informed Consent 34
[redacted]
9.2 Concurrent Therapies and Medical History 35
9.2.1 Prohibited Medications/Treatments 35
9.2.2 Escape Medications 36
9.2.3 Special Diet or Activities 36
9.3 Examination Procedures 36
9.3.1 Procedures to be Performed at the Study Visit with Regard to Study Objective 36
[redacted]

[redacted]

9.4 Schedule Of Visits, Measurements and Dosing 41
9.4.1 Scheduled Visit 41
9.4.2 Unscheduled Visits....41
9.4.3 Early Termination 42
9.5 Compliance with Protocol 42
9.6 Subject Disposition....42
9.6.1 Screened Subjects....42
9.6.2 Screen failed Subjects 42
9.6.3 Randomized Subjects 42
9.6.4 Discontinued Subjects 42
9.6.5 Completed Subjects....42
9.6.6 Withdrawn Subjects 42
9.7 Study Termination....42
9.8 Study Duration 43
9.9 Monitoring and Quality Assurance 43
10.0 ADVERSE EVENTS....43
10.1 Adverse Event 43
10.1.1 Severity 44
10.1.2 Relationship to Investigational Product....44
10.1.3 Expectedness 44
10.2 Serious Adverse Events....45
10.3 Procedures for Reporting Adverse Events 46
10.3.1 Reporting a Suspected Unexpected Adverse Reaction....46
10.3.2 Reporting a Serious Adverse Event....46
10.4 Procedures for Unmasking (if applicable)....46
10.5 Type and Duration of the Follow-up of Subjects after Adverse Events....47
11.0 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES 47
11.1 General Considerations 47
11.2 Hypotheses 47
11.3 Analysis Sets 48
11.4 Unit of Analysis 48
11.5 Efficacy Endpoints 49
11.5.1 Primary Efficacy Endpoint:....49

[redacted]

11.6 Safety Endpoints 52
11.7 Sample Size 52
11.8 Demographic and Baseline Characteristics 52
11.9 Efficacy Analysis 53
11.9.1 Primary Efficacy Analyses 53

[redacted]

11.10 Safety Analysis 53
11.11 Interim Analysis 54
11.12 Missing Data 54
11.13 Adjustment for Multiplicity 54
12.0 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES 55
12.1 Protection of Human Subjects 55
12.1.1 Subject Informed Consent 55
12.1.2 IRB Approval 55
12.2 Ethical Conduct of the Study 55
12.3 Subject Confidentiality 56
12.4 Documentation 56
12.4.1 Retention of Documentation 56
12.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product 56
12.5.1 Labeling/Packaging 56
12.5.2 Storage of Investigational Product 57
12.5.3 Accountability of Investigational Product 57
12.5.4 Return or Disposal of Investigational Product 57
12.6 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs) 57
12.7 Handling of Biological Specimens 57
12.8 Publications 58

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
BID	Twice daily
BCDVA	Best-corrected distance visual acuity
cd/m^2	Candela per square meter
CFR	Code of Federal Regulations
CI	Confidence interval
eCRF	Electronic case report form
D	Diopter
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
[redacted]	[redacted]
[redacted]	[redacted]
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional review board
IUD	Intrauterine device
HIPAA	Health Information Portability and Accountability Act
LASEK	Laser-assisted epithelial keratomileusis
LASIK	Laser-assisted in-situ keratomileusis
logMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
mmHG	Millimeters of mercury
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-the-counter
PP	Per protocol
PRK	Photorefractive keratectomy
PT	Preferred term
RGP	Rigid gas permeable
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
VA	Visual acuity

2.0 INTRODUCTION

Presbyopia is defined by a loss in the ability of the eye to adjust its focal length so that objects at different distances produce focused images on the retina. As the eye ages, the lens of the eye becomes less able to change shape. Hardening of the lens, along with weakening of the ciliary muscles, plays a major role in the pathogenesis of presbyopia and leads to symptoms such as blurred vision, eye strain and headache after reading or computer use (Truscott 2009; Helmholtz 1855; Ostrin and Glasser 2007; Scarcelli 2011).

Presbyopia affects most people over 45 years of age and continues to worsen until approximately 65 years of age. Based on data from 228 countries, it was estimated that in 2005, presbyopia affected more than 1 billion people worldwide. Presbyopia is projected to increase to 1.78 billion people by 2050. More than half of the people with this condition do not have adequate treatment options, which results in some level of disability when performing tasks that require near visual acuity (Holden 2008).

Current treatments available for presbyopia include the use of reading glasses, contact lenses, or refractive surgery (including laser) or intraocular lens (IOL) surgery.

Pharmaceutical therapies have been explored but, thus far, continue to be limited in treating presbyopia without being associated with undesirable adverse effects (Gilmartin 1995). Pilocarpine ophthalmic solution 1.25% is the only approved pharmacologic treatment for presbyopia in adults to date.

Both Aceclidine and Brimonidine have been used extensively in humans for ophthalmic indications. Aceclidine is a parasympathomimetic miotic agent that is approved for lowering IOP in Europe. In 1969, a 2% solution (dosed four times a day) of Aceclidine was approved in several European countries for the treatment of glaucoma. Furthermore, Aceclidine has been used at concentrations of up to 4% in humans. Brimonidine is an alpha adrenergic drug that was approved for human use in the US in 1996. Brimonidine has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow. Brimonidine at concentrations of up to 0.2% typically dosed twice daily has been shown to be generally safe and effective. Notably, the concentrations of Aceclidine and Brimonidine in LNZ-101 formulation in this study [redacted] are substantially lower than the concentrations of these agents that are in clinical use.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

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

[redacted]

5.0 OVERALL STUDY DESIGN

This is a [redacted] 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.

Visit 1 (Screening, Day -60 to -4): Subjects will be screened through ophthalmic assessments using best corrected distance visual acuity (BCDVA) tests. [redacted]

Visit 2 (Randomization, Day 1): Visit 1 ophthalmic assessments will be repeated at Visit 2 per the Schedule of Visits and Measurements. Following the pre-treatment, baseline assessments, qualified subjects will be randomized [redacted] to one of the following study arms:

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

[redacted] Primary efficacy and safety assessments will be performed.

[redacted]

6.0 STUDY POPULATION

Approximately 222 healthy adult subjects from 45 to 75 years of age (inclusive) with presbyopia who do not have any conditions, in the investigator's opinion, that may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation.

6.1 Inclusion Criteria

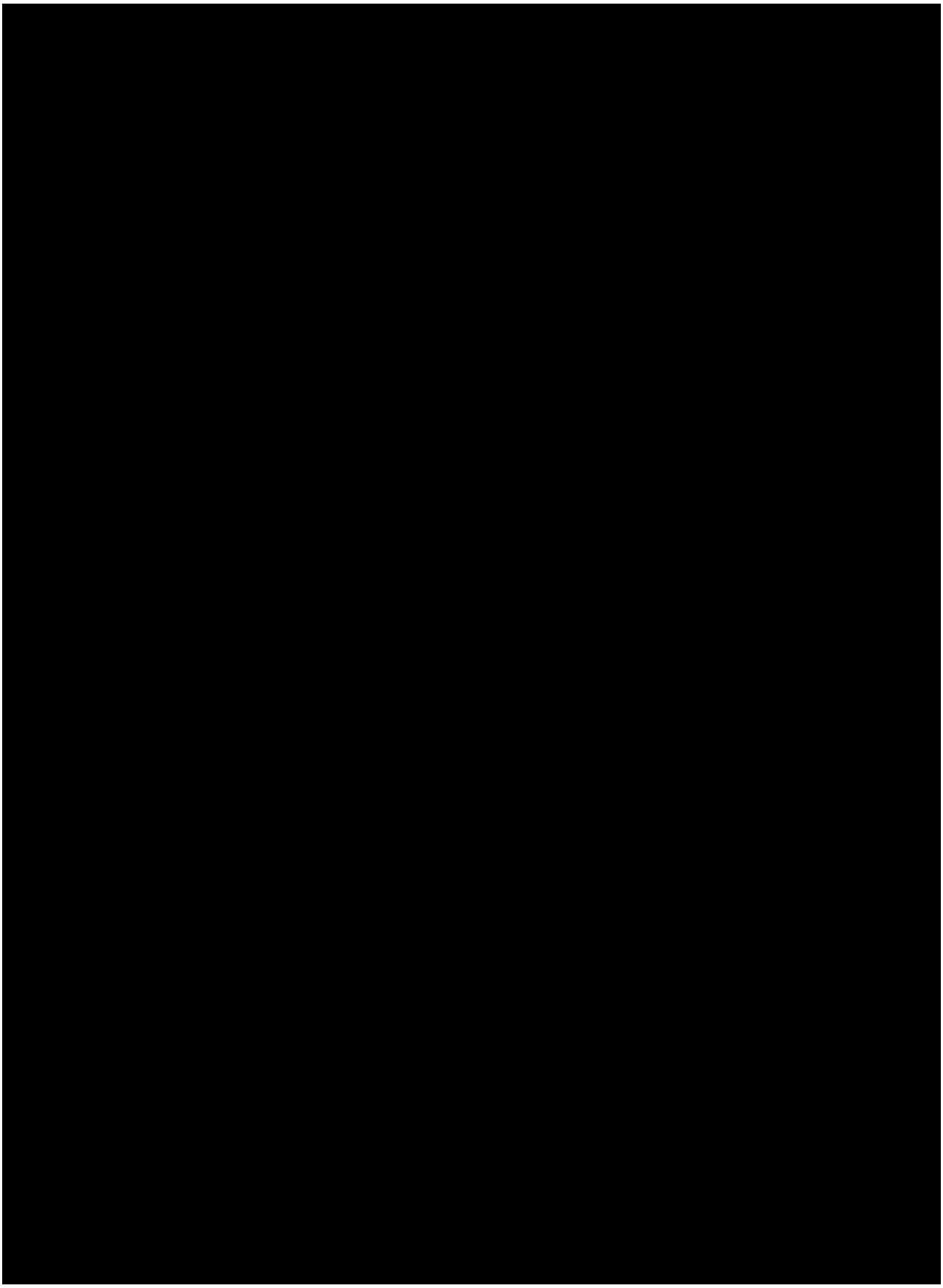
Subjects must:

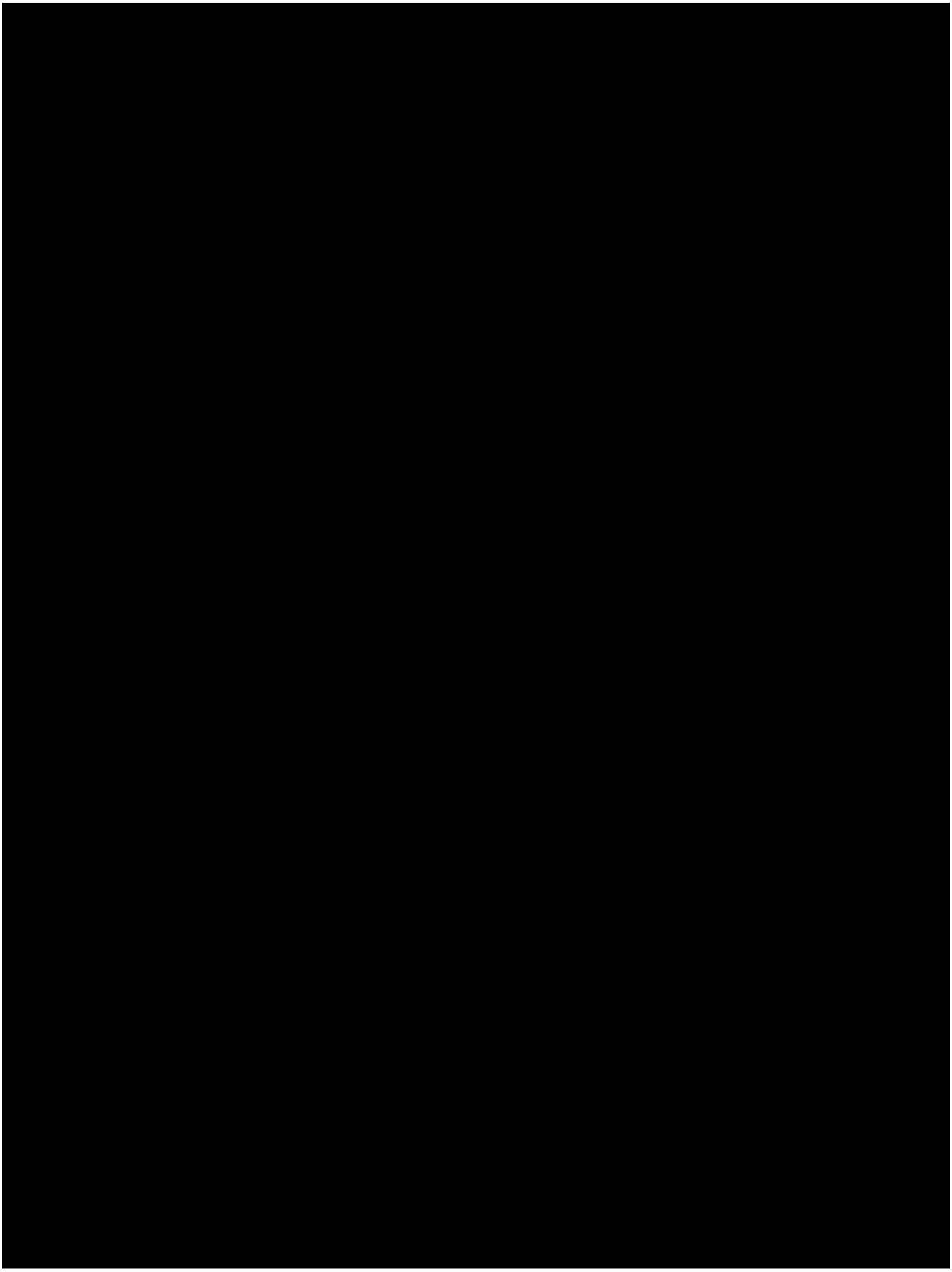
1. Be able and willing to provide written informed consent and sign a Health Information Portability and Accountability Act (HIPAA) form prior to any study procedure being performed;

2. Be able and willing to follow all instructions and attend all study visits;
3. Be 45-75 years of age of either sex and any race or ethnicity at Visit 1;

6.2 Exclusion Criteria

1. Subject must not be a female of childbearing potential who is currently pregnant, nursing, or planning a pregnancy;
2. Subject must not have known contraindications or sensitivity to the use of any of the study medications or their components;
3. Neither eye can have an active ocular infection at Visit 1 or at Visit 2 (bacterial, viral, or fungal), positive history of an ocular herpetic infection, preauricular lymphadenopathy, or ongoing, active ocular inflammation (e.g., moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis);





[redacted]

6.4 Withdrawal Criteria

Subjects will be withdrawn from the study if any of the following criteria are met:

- Be a female of childbearing potential who is currently pregnant, nursing, or planning a pregnancy; tests positive to a pregnancy test; or refuses to use an adequate method of contraception for the duration of the study;
- Have an active ocular infection (bacterial, viral, or fungal), active ocular inflammation (e.g. moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis) in either eye.
- Subjects may also be withdrawn from the study for the following reasons:
  - Adverse event (AE)
  - Lost to follow-up

[redacted]

- Withdrawal of consent by subject
- Investigator's discretion
- Death
- Subject not adequately following required study procedures
- Study terminated by the Sponsor
- Other

Subject withdrawals will be documented on the subject's source document.

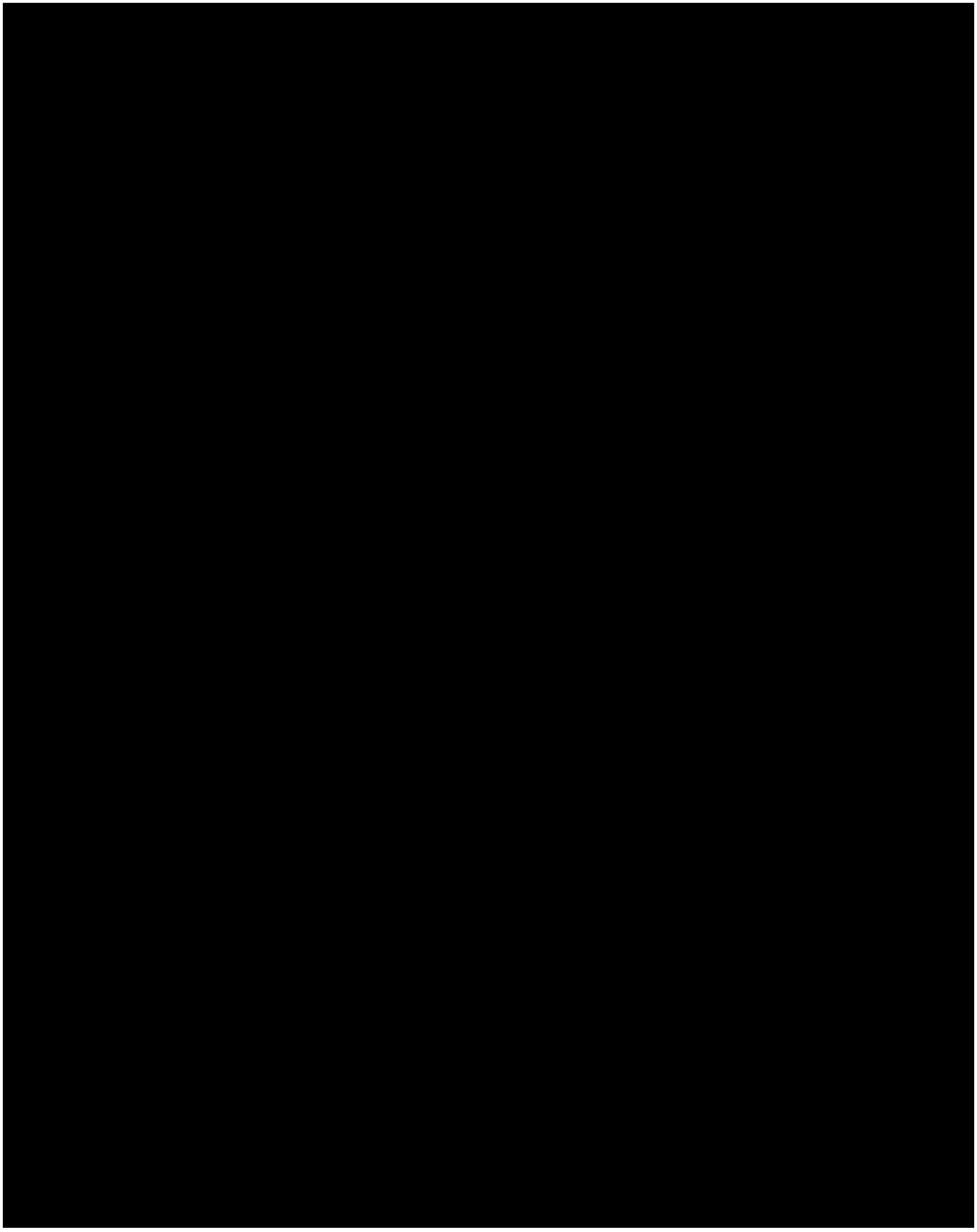
7.0 STUDY PARAMETERS

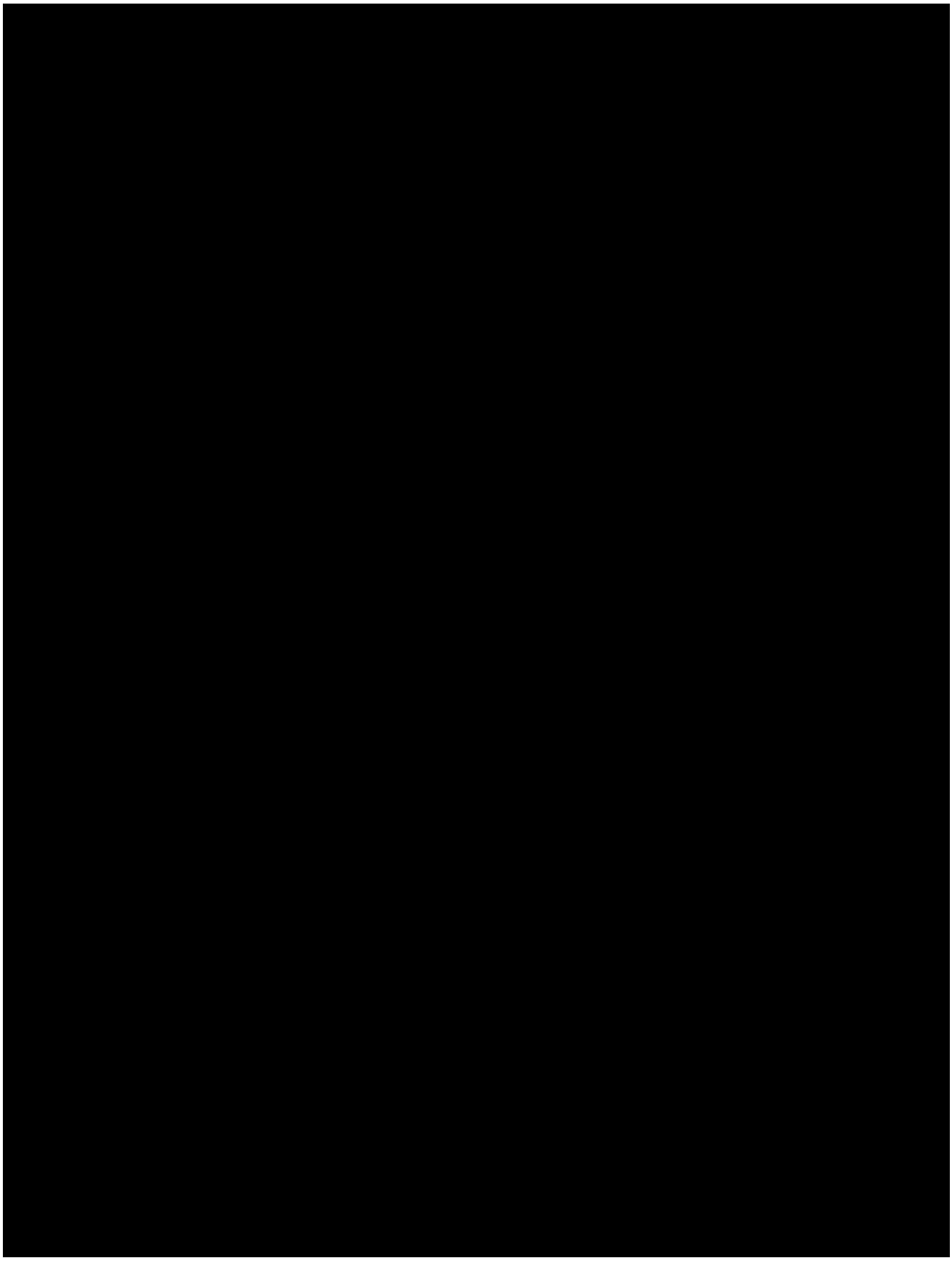
7.1 Efficacy Endpoints

Primary Efficacy Endpoint:

- Percentage of subjects who 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]





[redacted]

Criteria for Efficacy

Changes in BCDVA at 40 cm distance will be calculated as the difference, in logMAR units, between the post-treatment monocular (study eye) minus the pre-treatment baseline monocular (study eye) at Visit 2. A 3-line improvement or greater in BCDVA at 40 cm is considered clinically meaningful.

7.2 Safety Endpoints

- Adverse events (AE) (reported, elicited, and observed)
- Pregnancy test [redacted]

- Monocular and binocular BCDVA (normal and low-luminance)
- Slit lamp biomicroscopy
- IOP
- Dilated fundus exam [redacted]
- Conjunctival redness

8.0 STUDY MATERIALS

8.1 Study Treatments

8.1.1 Investigational Product

The study treatments are as follows:

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

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

Vehicle ophthalmic solution will be provided in a sterile container.

8.1.2 Instructions for Use and Administration

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).

[redacted]

A new clinical kit will be assigned to each subject [redacted].

[redacted]

[redacted]

9.0 STUDY METHODS AND PROCEDURES

9.1 Subject Entry Procedures

9.1.1 Overview

Subjects as defined by the criteria in Section 6.1 and Section 6.2 will be considered for entry into this study.

[redacted]

9.1.2 Informed Consent

Prior to a subject's participation in the trial (e.g. changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent (and/or assent) using an informed consent form (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted IRB.

[redacted]

9.2 Concurrent Therapies and Medical History

The use of any concurrent medication, prescription, or over-the counter taken within 30 days of Visit 1, is to be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken.

All significant current and prior ocular medical and surgical history is to be recorded on the subject's source document and corresponding eCRF. All current and prior significant general medical and surgical history is to be recorded on the subject's source document and corresponding eCRF.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

9.2.1 Prohibited Medications/Treatments

Soft contact lenses must be removed at least 7 days prior to study Visit 1 and during the study, and rigid gas permeable (RGP) contact lenses must be removed at least 14 days prior to study Visit 1 and during the study.

9.2.2 Escape Medications

Not applicable.

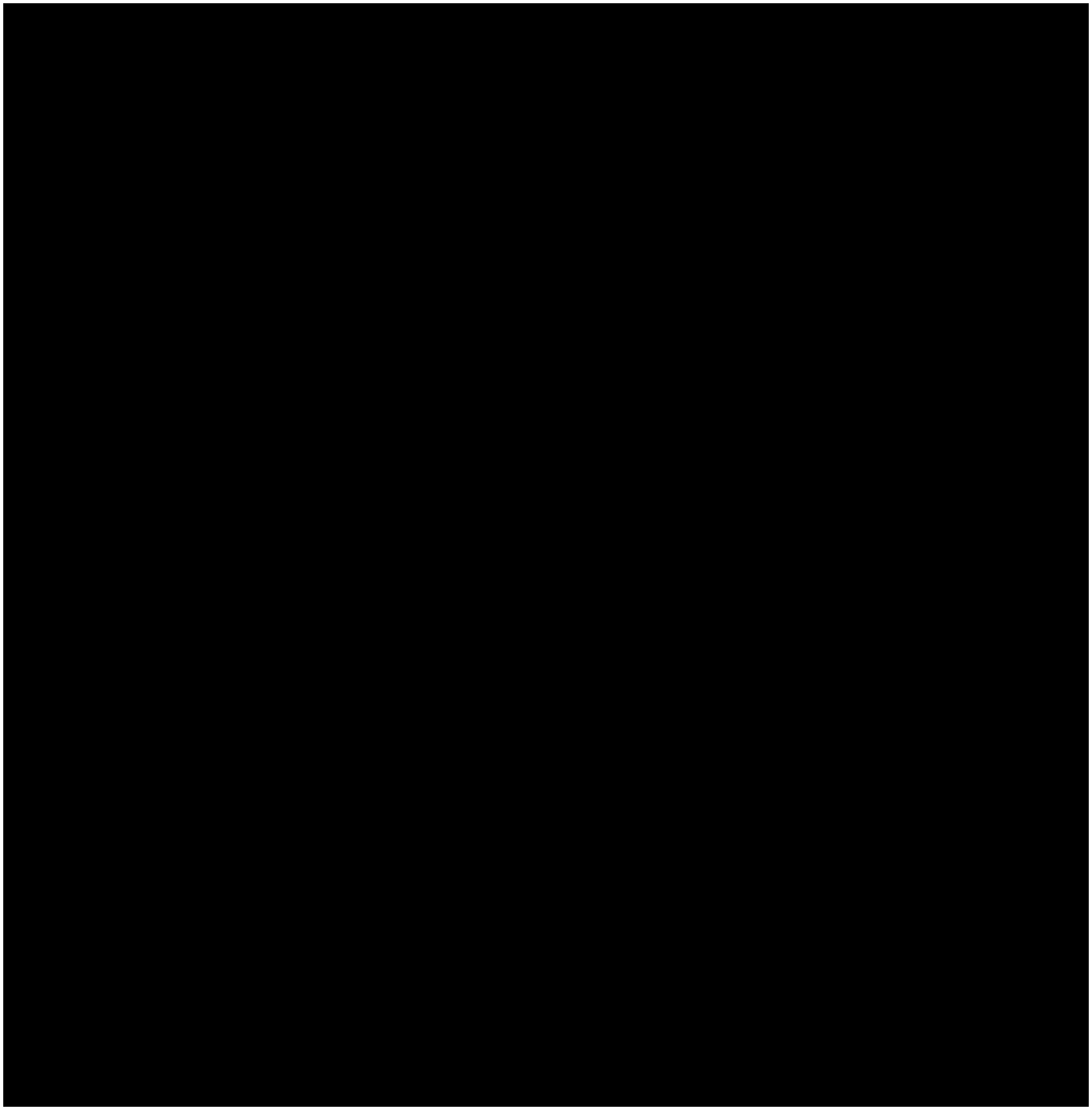
9.2.3 Special Diet or Activities

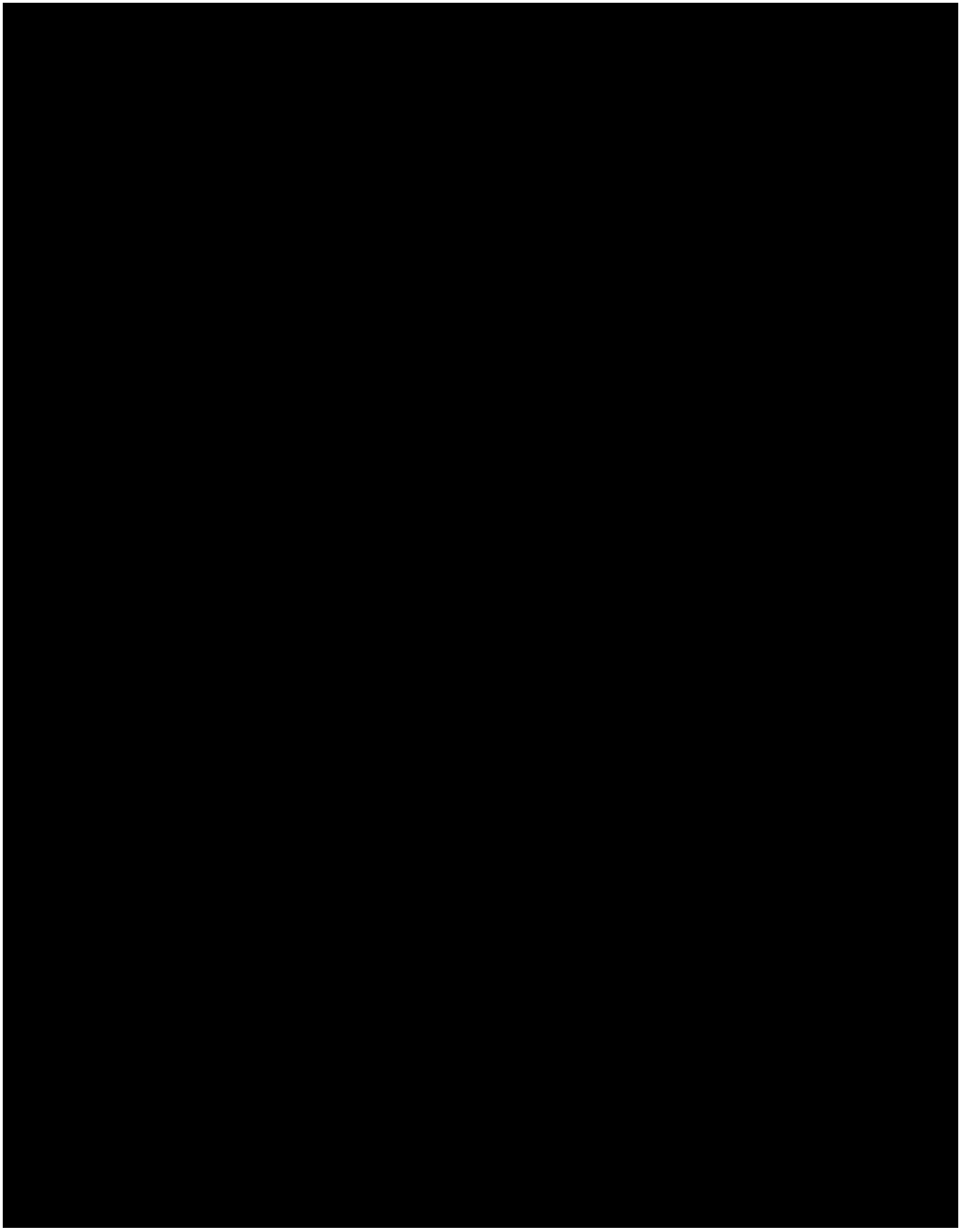
Not applicable.

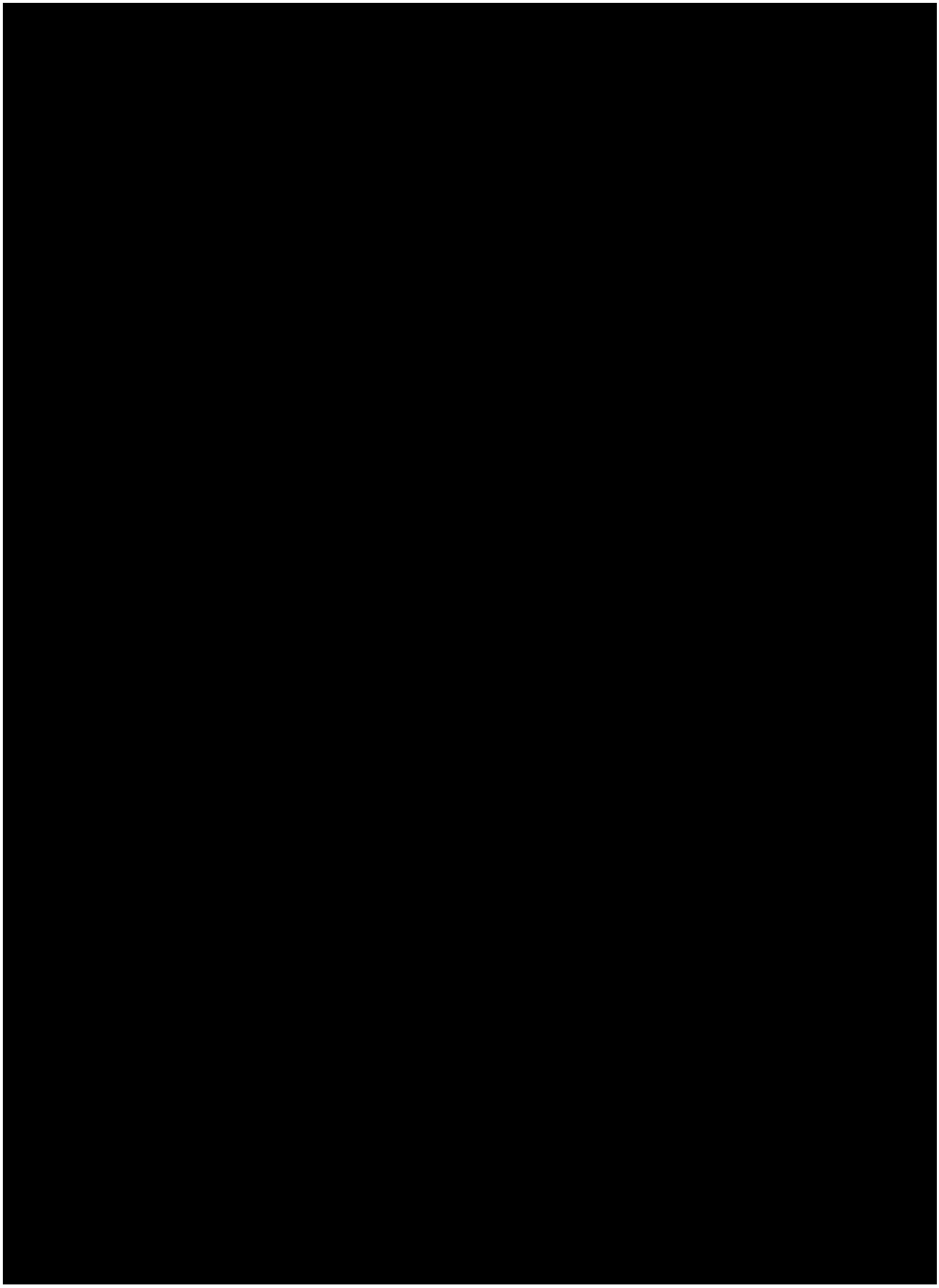
9.3 Examination Procedures

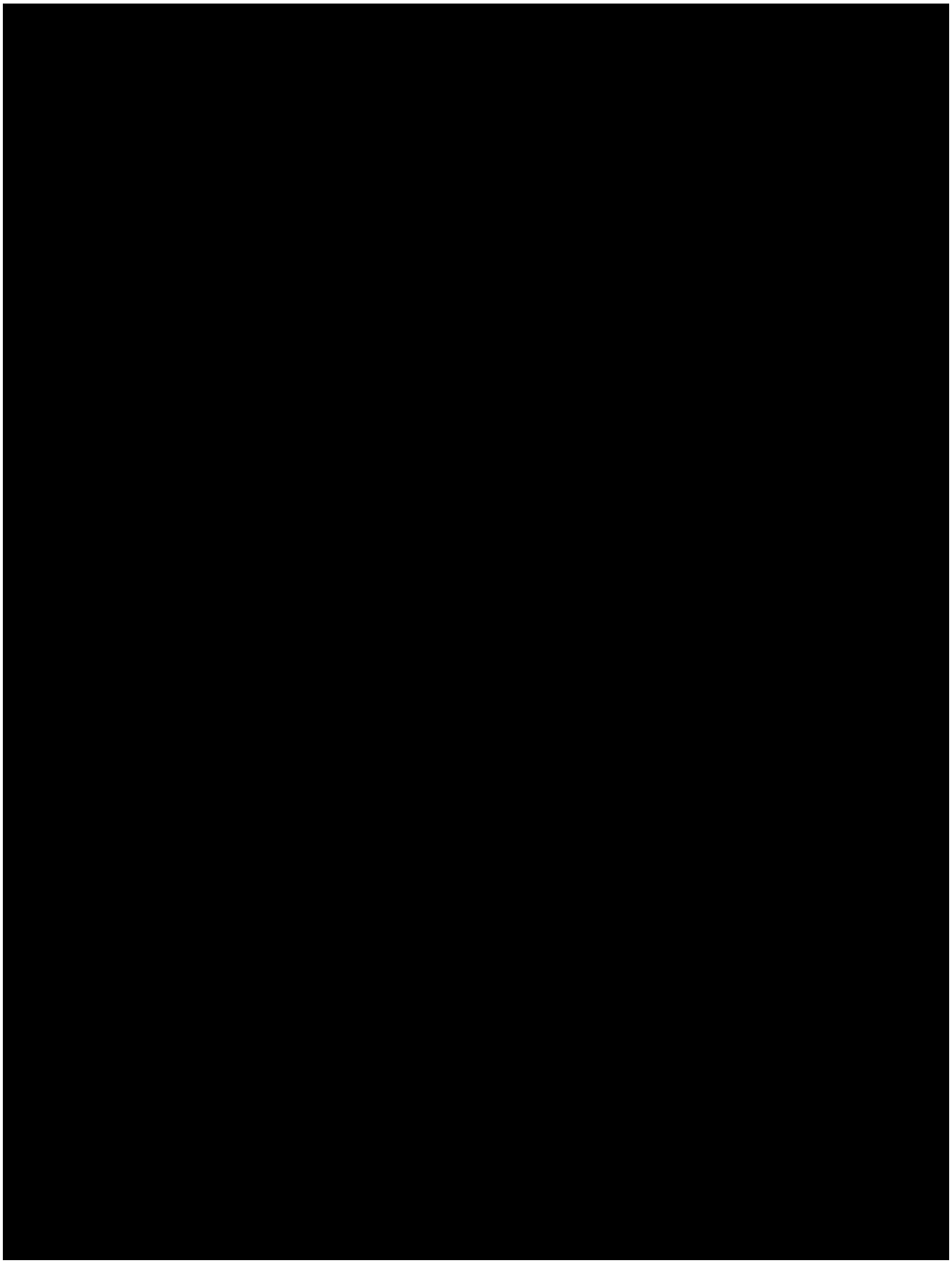
9.3.1 Procedures to be Performed at the Study Visit with Regard to Study Objective

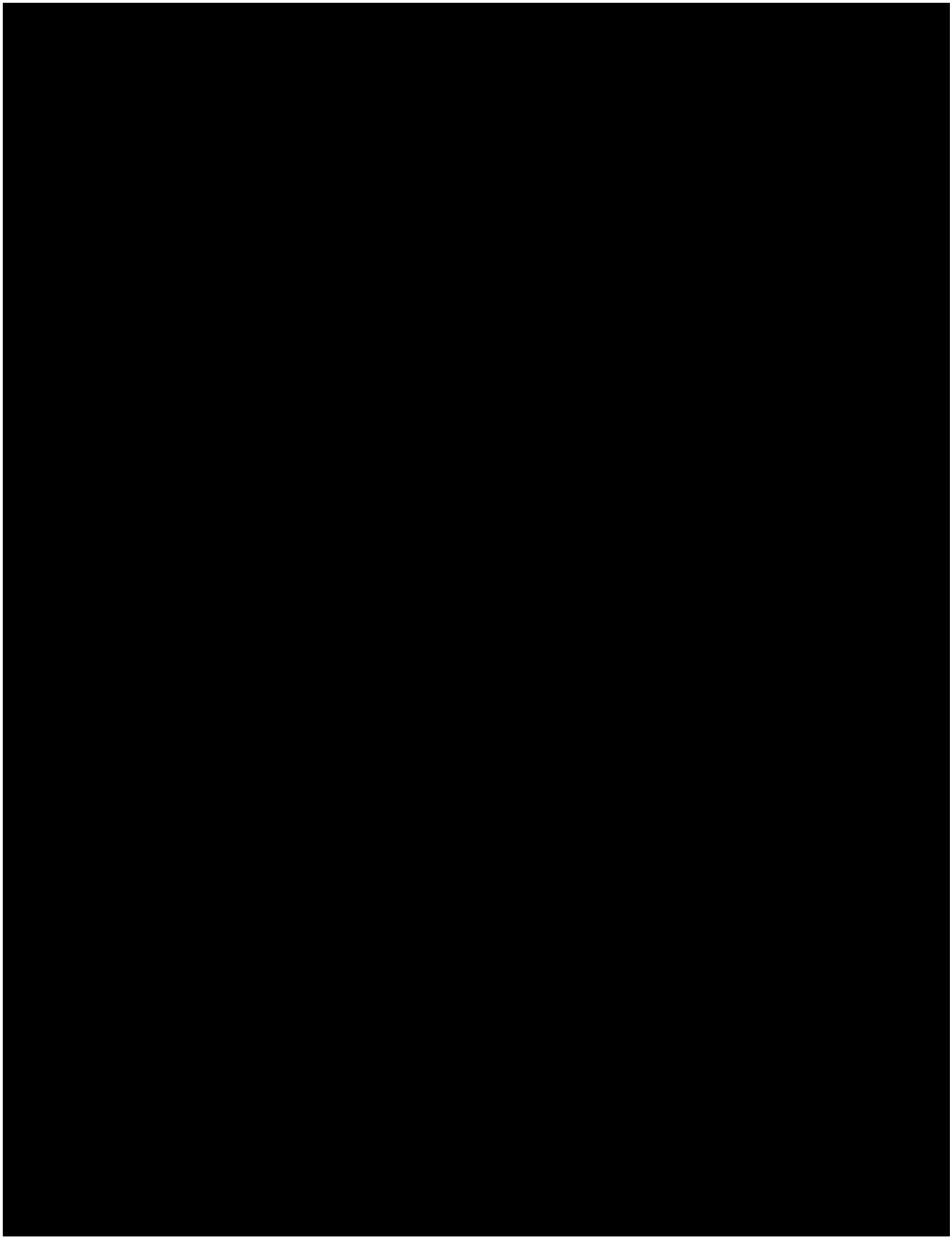
The following procedures should be conducted at each study visit in the following order.











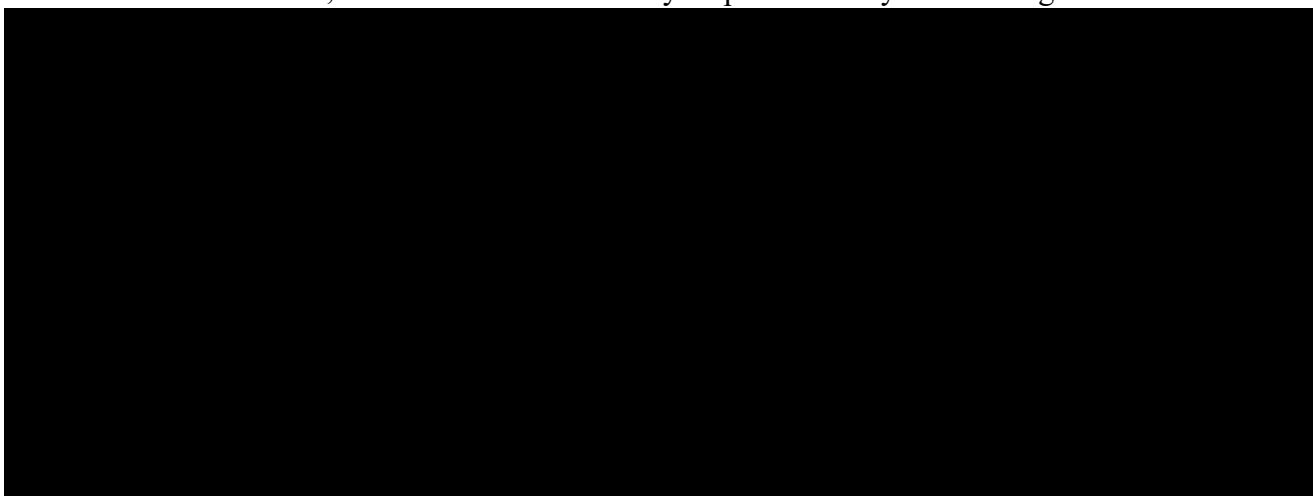
9.4 Schedule Of Visits, Measurements and Dosing

9.4.1 Scheduled Visit

Refer to Appendix 1: Schedule of Visits and Measurements for a schedule of measurements at each visit.

9.4.2 Unscheduled Visits

In the case of an AE, an Unscheduled Visit may be performed by the Investigator.



The Investigator may perform additional assessments, if needed. All additional assessments will be documented in the subject's source document.

9.4.3 Early Termination

Participants who prematurely discontinue from the study after administration of the study drug will be encouraged to complete an early termination (ET) visit.

9.5 Compliance with Protocol

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s), such as Food and Drug Administration (FDA) GCP Regulations and Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312, as appropriate.

9.6 Subject Disposition

9.6.1 Screened Subjects

Subject who has completed the Informed Consent process and if eligible to proceed with additional assessments to ensure candidacy at Visit 1 (Screening Visit).

9.6.2 Screen failed Subjects

Screened subject who does not meet the inclusion/exclusion criteria at any time prior to randomization at Visit 2.

9.6.3 Randomized Subjects

Subject who has signed the ICF, been issued a unique 6-digit subject number and has been randomized to receive investigational product at Visit 2. Once randomized, the subject is enrolled in the study.

9.6.4 Discontinued Subjects

Randomized subject who discontinues participation in the trial prior to the last study procedure [redacted]

Prior to discontinuing a subject, every effort should be made to obtain as much follow-up data as possible, and to retrieve all study materials. Adverse events (AEs) will be followed as described in Section 10.

9.6.5 Completed Subjects

A completed subject is one who has not been discontinued from the study.

9.6.6 Withdrawn Subjects

A subject may be withdrawn for meeting any of the withdrawal criteria as described in Section 6.3.

Prior to discontinuing a subject, every effort should be made to obtain as much follow-up data as possible, and to retrieve all study materials. Adverse events (AEs) will be followed as described in Section 10.0.

9.7 Study Termination

The study may be terminated at any time by the investigator, the sponsor, and/or Ora with appropriate notification.

9.8 Study Duration

This study is [redacted] a total duration of approximately 9 weeks.

9.9 Monitoring and Quality Assurance

During the course of the study an Ora monitor, or designee, will make routine site visits to review protocol compliance, assess IP accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, and Ora, Inc. quality assurance and/or its designees, and the study sponsor may carry out on-site inspections and/or audits that may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

10.0 ADVERSE EVENTS

10.1 Adverse Event

Adverse events will be monitored throughout the study. At each visit, the Investigator, or designee, will query for adverse events by asking subjects general, non-directed questions such as:

"How have you been feeling since the last visit?" [redacted]

"Have there been any changes in how you are feeling since you came in today"? [redacted]

Directed questioning and examinations will be done as appropriate.

An AE is defined as any untoward medical occurrence associated with the use of an 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 spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded in the subject's source document and eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to IP, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

All AEs will be collected from the time a subject signs the ICF through the subject's study exit visit.

10.1.1 Severity

The 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 patient/subject. The assessment of severity is made irrespective of relationship to IP 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.

10.1.2 Relationship to Investigational Product

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

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

"Suspected adverse reaction" means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g. angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g. tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

10.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP 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 IP.

AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological (or other) properties of the product but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE. The medical monitor will review and determine the expectedness of any serious adverse event (SAE) following the investigator's assessment. The final classification of an AE is subject to the sponsor's determination.

10.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if < 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/Phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g. intra-ocular hemorrhage, retinal detachment, central corneal ulcer, or damage to the optic nerve).
- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate subject source document and eCRF.

10.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities.

10.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported by the investigator to Ora and the sponsor within 24 hours of becoming aware of the event. All information relevant to the SAE must be recorded on the appropriate source document, SAE Report Form, and eCRF. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to the information reported on the source document, SAE Report Form, and eCRF. All subjects experiencing a SAE must be followed-up with and the outcome reported.

In the event of a SAE, the investigator must notify Ora and the sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the study sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP; and inform the IRB of the AE within their guidelines for reporting SAEs.

[redacted]

10.4 Procedures for Unmasking (if applicable)

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. When possible (i.e. in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking the IP.

10.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The investigator will follow unresolved AEs to resolution, until the subject is lost to follow-up or until the AE is otherwise explained. Resolution means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the source document with the status noted.

If the investigator becomes aware of any new information regarding a SAE (i.e. resolution, change in condition, or new treatment), a new SAE Report Form must be completed and faxed/emailed to Ora and/or the study sponsor within 24 hours. The original SAE Report Form is not to be altered. The SAE Report Form should describe whether the event has resolved or continues and how the event was treated.

11.0 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

11.1 General Considerations

In general, quantitative/continuous data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum). Qualitative/categorical data will be summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level.

For all variables, baseline is defined as the last measurement taken prior to the administration of first dose of study drug at Visit 2. Change from baseline will be calculated as follow-up measure minus baseline measure.

[redacted]

[redacted]

11.3 Analysis Sets

Full Analysis Set (FAS) – The 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.

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

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.

11.4 Unit of Analysis

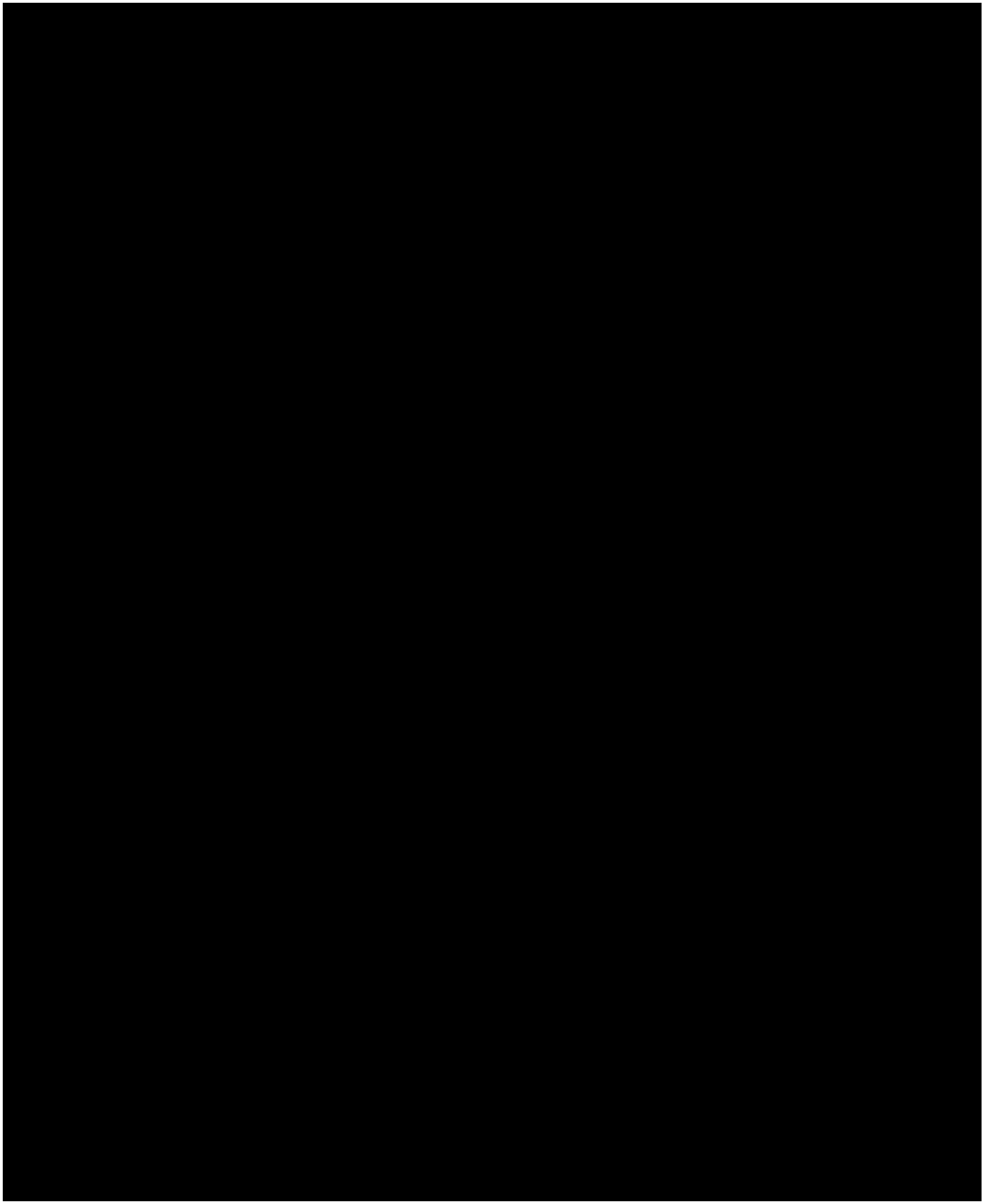
The study eye will be used for all monocular efficacy analyses. The qualified fellow eye will be used in additional binocular analyses as specified. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

[redacted]

11.5 Efficacy Endpoints

11.5.1 Primary Efficacy Endpoint:

- Percentage of subjects who 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]

11.6 Safety Endpoints

The safety endpoints are:

- Adverse events (AE) (reported, elicited, and observed)
- Pregnancy test [redacted]
- Monocular and binocular BCDVA (normal and low-luminance)
- Slit lamp biomicroscopy
- IOP
- Dilated fundus exam [redacted]
- Conjunctival redness

11.7 Sample Size

A sample size of 222 subjects (74 per arm) yields >99% power to establish superiority of LNZ101/LNZ100 to vehicle in the proportion of study eyes demonstrating a ≥ 3-line (15-letter) improvement or greater from baseline in BCDVA at 40 cm and no loss in BDVA ≥ 1 line (5 letters) at 4 m [redacted]

11.8 Demographic and Baseline Characteristics

Subject demographics including age, gender, race, ethnicity, and iris color will be presented using continuous/categorical summary statistics as appropriate.

11.9 Efficacy Analysis

11.9.1 Primary Efficacy Analyses

The primary efficacy endpoint in this study is the percentage of study eyes with a ≥ 3-line (15-letter) improvement in BCDVA at 40 cm from baseline and no loss in best distance corrected visual acuity ≥ 1 line (5-letter) at 4 m [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% confidence intervals (CIs) and p-values will be presented.

Treatment comparisons will also be made using Pearson's chi-squared test or Fisher's exact test if any of the expected cell counts are less than five as a sensitivity analysis to the primary model above.

Analyses will be repeated using the FAS with missing data imputed as failures and FAS and PP sets with observed data. Tipping point analysis may be performed.

[redacted]

11.10 Safety Analysis

All safety data will be analyzed using the Safety set. Safety of LNZ101/LNZ100 will be assessed by the review of all safety parameters.

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms and be presented in a data listing. Treatment emergent Aes (TEAEs), those that occur after the first dose of study drug, will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Similar summaries will also be presented for expected and unexpected TEAEs, treatment emergent SAEs, TEAEs related to the study drug, and TEAEs by severity. When reporting the incidence of Aes, a subject will only be counted once if they ever experience an event within the SOC and ever experience the individual PT within each treatment group. . Ocular and non-ocular events will be summarized separately.

Actual results and changes from baseline results in monocular and binocular BCDVA (normal and low-luminance), slit lamp biomicroscopy, IOP, dilated fundus examination, and conjunctival redness, will be summarized descriptively at each visit by treatment group.

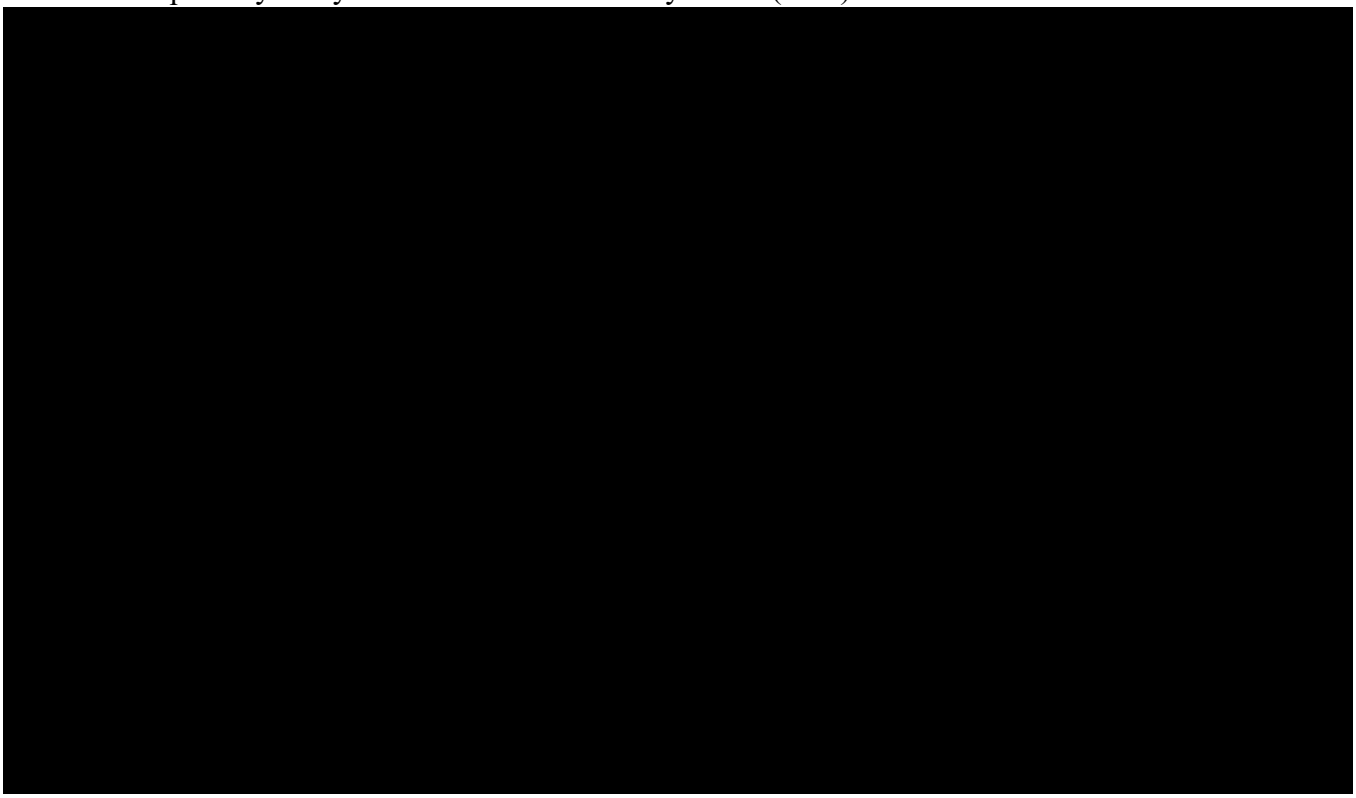
Full details of the safety analyses will be specified in the formal SAP.

11.11 Interim Analysis

No interim analysis is planned for this study.

11.12 Missing Data

The primary analysis will use the Full Analysis Set (FAS) with intercurrent events



11.13 Adjustment for Multiplicity

There is no adjustment necessary for the primary endpoint because only one time point is being considered for the primary analysis.

12.0 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current GCPs, including the ICH Guidelines, and will, in general, be consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of Ips in the countries involved will be adhered to.

12.1 Protection of Human Subjects

12.1.1 Subject Informed Consent

Informed consent must take place before any study-specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study.

All ICFs must be approved for use by the sponsor and receive approval/favorable opinion from an IRB prior to their use. If the ICF requires revision (e.g. due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB and that it is read, signed, and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by Ora and/or the sponsor and provided in writing by Ora and/or the sponsor prior to the consent process.

12.1.2 IRB Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB-approved version of the ICF will be used.

12.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

12.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the sponsor, the IRB approving this study, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed in, but the subject's identity will not be disclosed in these documents.

12.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the eCRFs serves as the investigator's record of a subject's study-related data.

12.4.1 Retention of Documentation

All study-related correspondence, patient records, consent forms, records of the distribution and use of all Ips, and copies of case report forms should be maintained on file for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

12.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

12.5.1 Labeling/Packaging

Investigational drug will be packaged and labeled into clinical kits, following the randomization list generated prior to the start of the study. Each clinical kit will be uniquely identified by a 5-digit kit number.

The primary packaging of the LNZ101, LNZ100, and Vehicle Ophthalmic Solution will be blow-fill-seal ampoules. [redacted]

Clinical label texts for the primary packaging and secondary packaging (clinical kits) meet applicable regulatory requirements and include the statement "Caution: New Drug-Limited by Federal Law to Investigational Use.

12.5.2 Storage of Investigational Product

Investigational drug must be stored in a secure area of the investigative site, accessible only to Investigator or designees [redacted] The investigational product will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. All investigational drugs will be returned to inventory after use.

12.5.3 Accountability of Investigational Product

The investigational product is to only be administered by a trained study technician delegated by the principal Investigator,) and is to only be used in accordance with this protocol. The investigational product must only be distributed to subjects properly qualified under this protocol to receive investigational product.

The Investigator must keep an accurate accounting of the investigational product received from the supplier. This includes the amount of investigational product administered to subjects and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the investigational product.

12.5.4 Return or Disposal of Investigational Product

All IPs will be returned to the sponsor or their designee or destroyed. The return or disposal of IP will be specified in writing. Any remaining IP will be collected from subjects before study exit.

12.6 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's source document, eCRF, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g. by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when by adding to the correction his/her initials as well as the date of the correction.

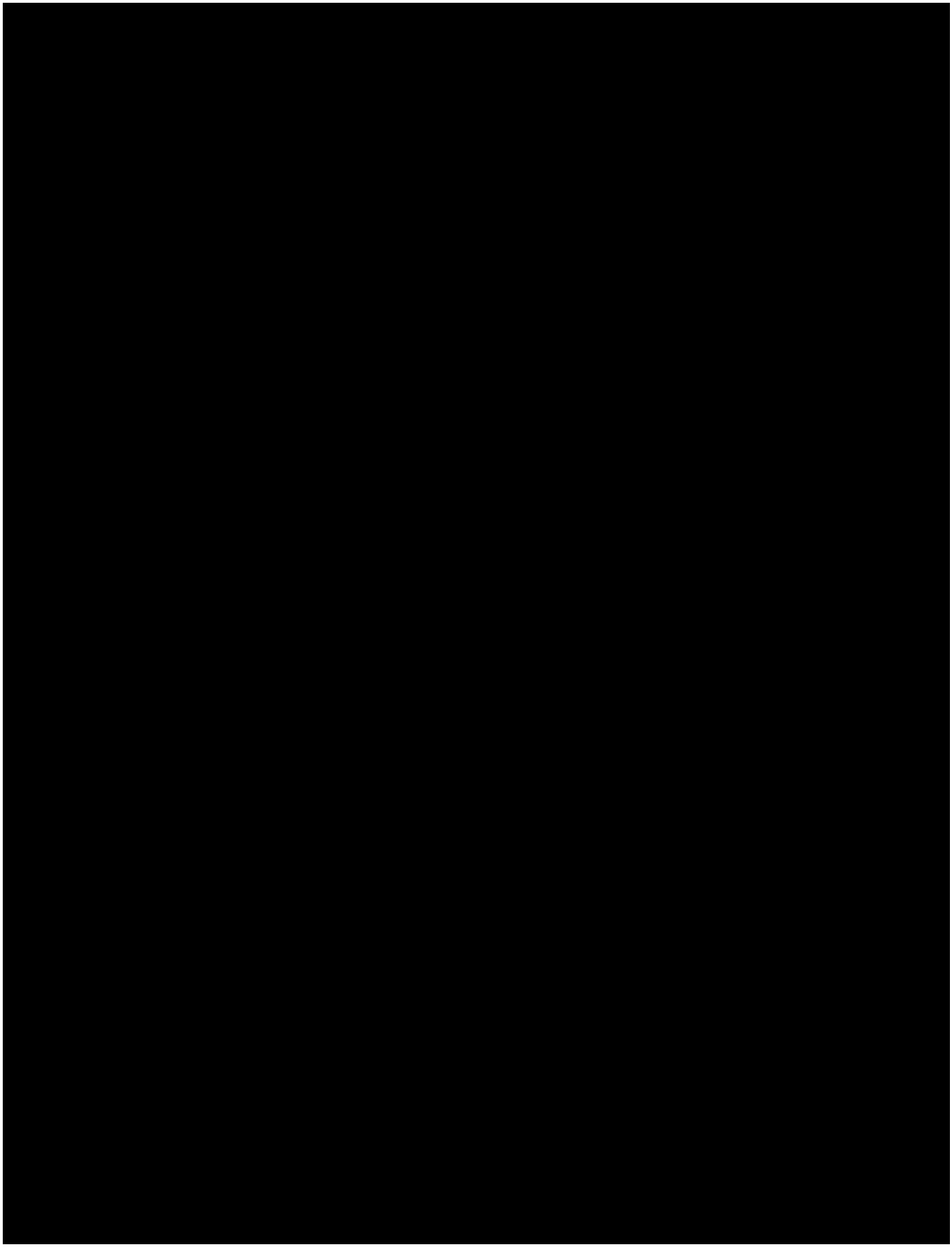
12.7 Handling of Biological Specimens

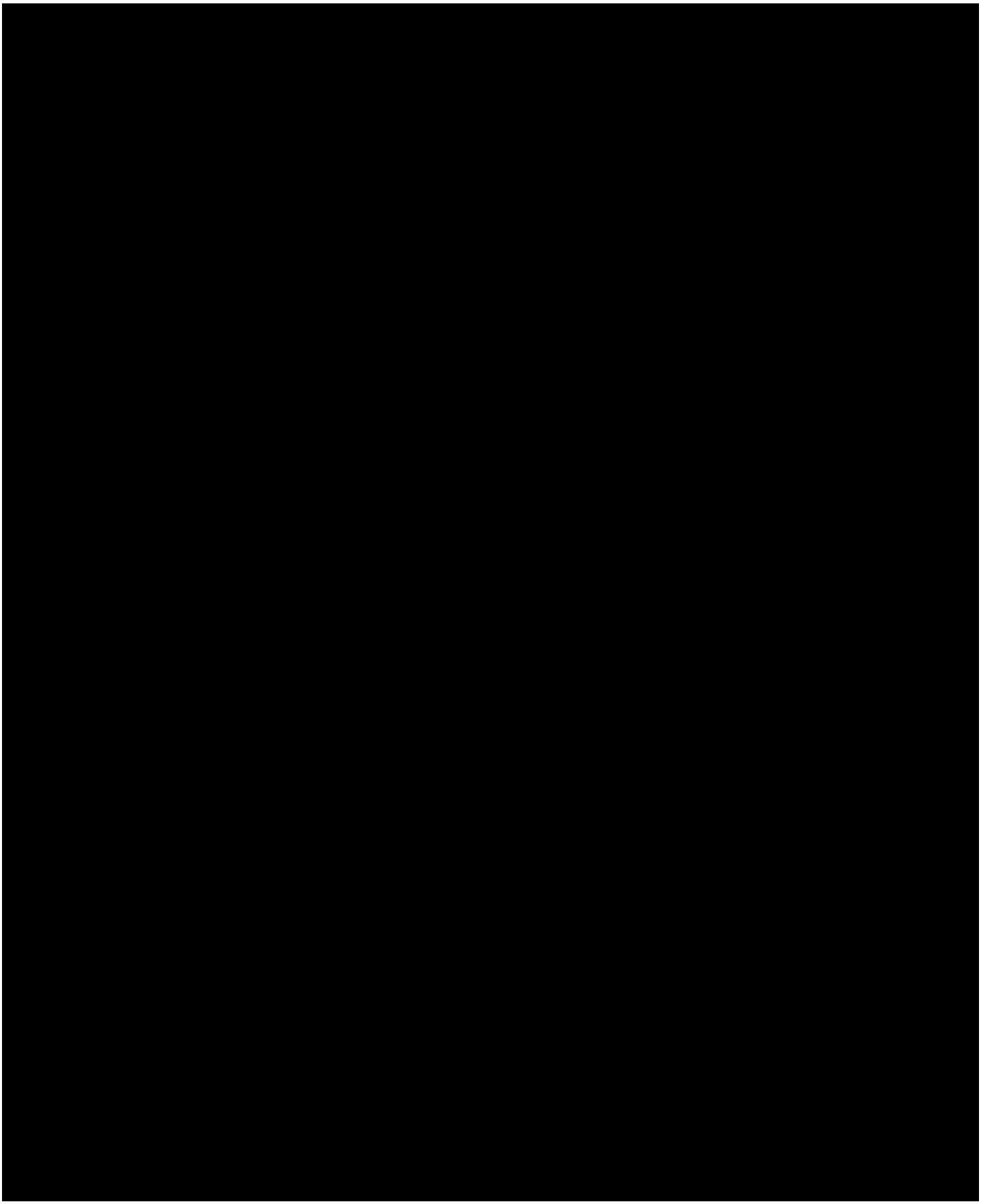
Not applicable.

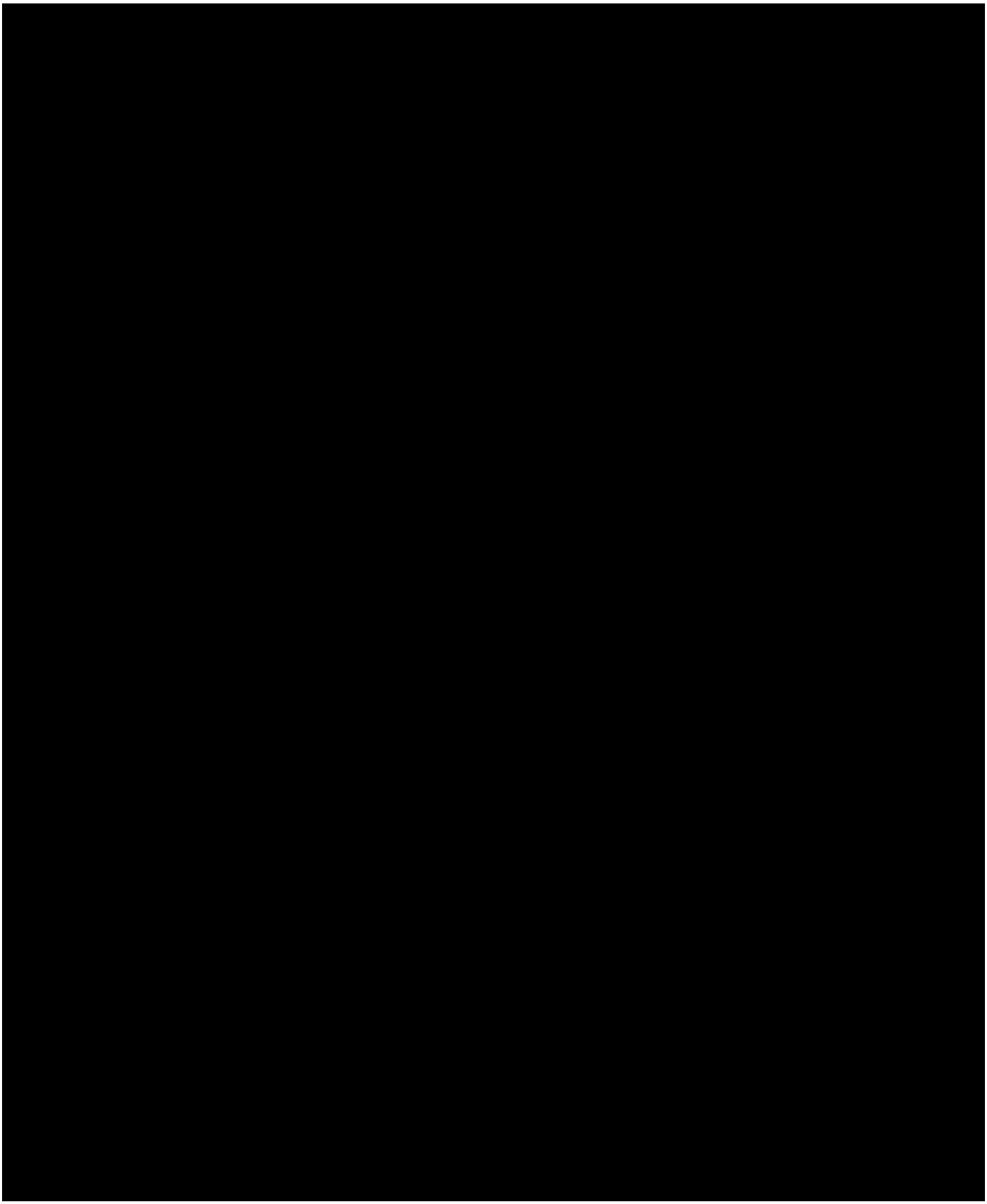
12.8 Publications

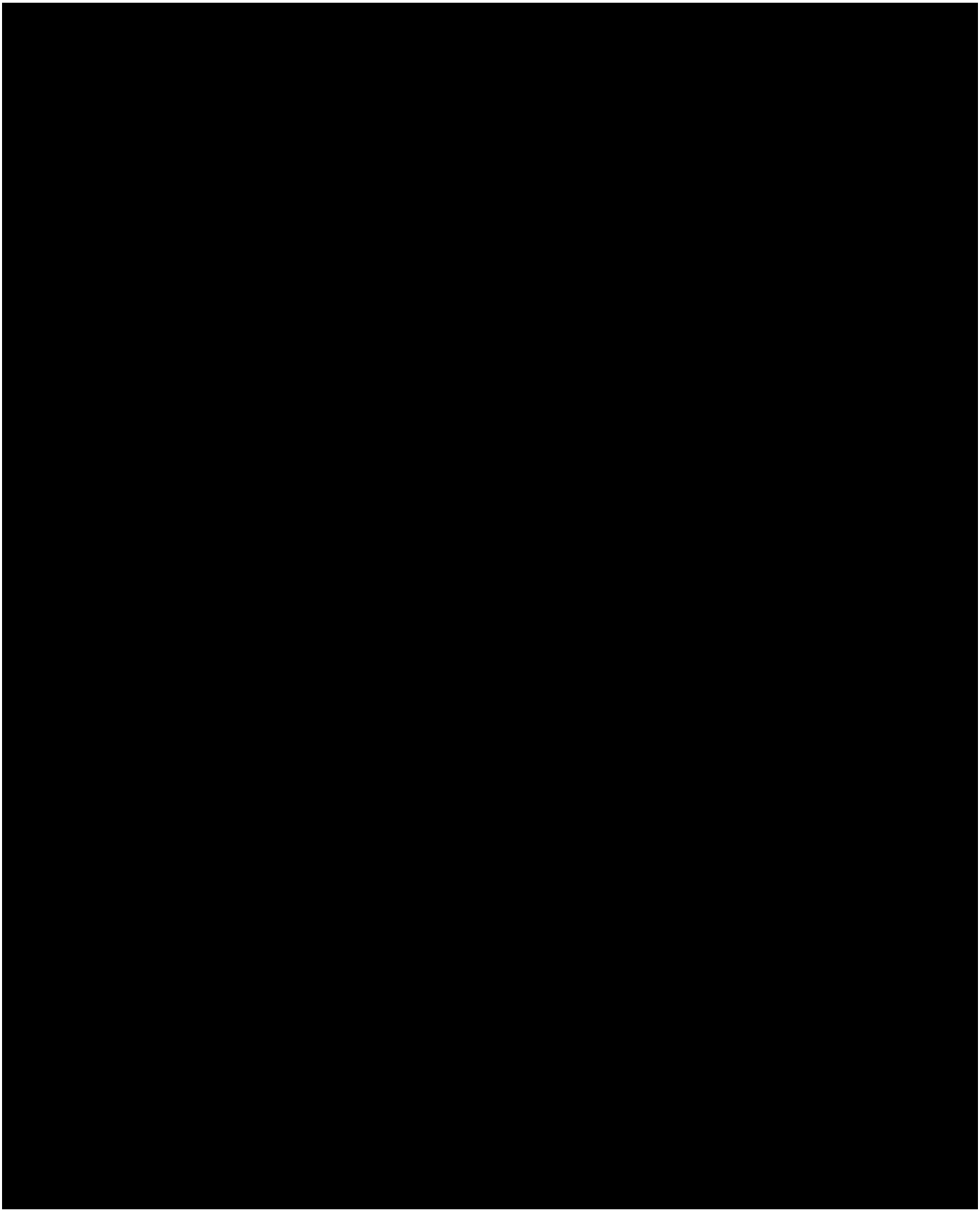
Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Ora and the study sponsor will have the final decision regarding the manuscript and publication.

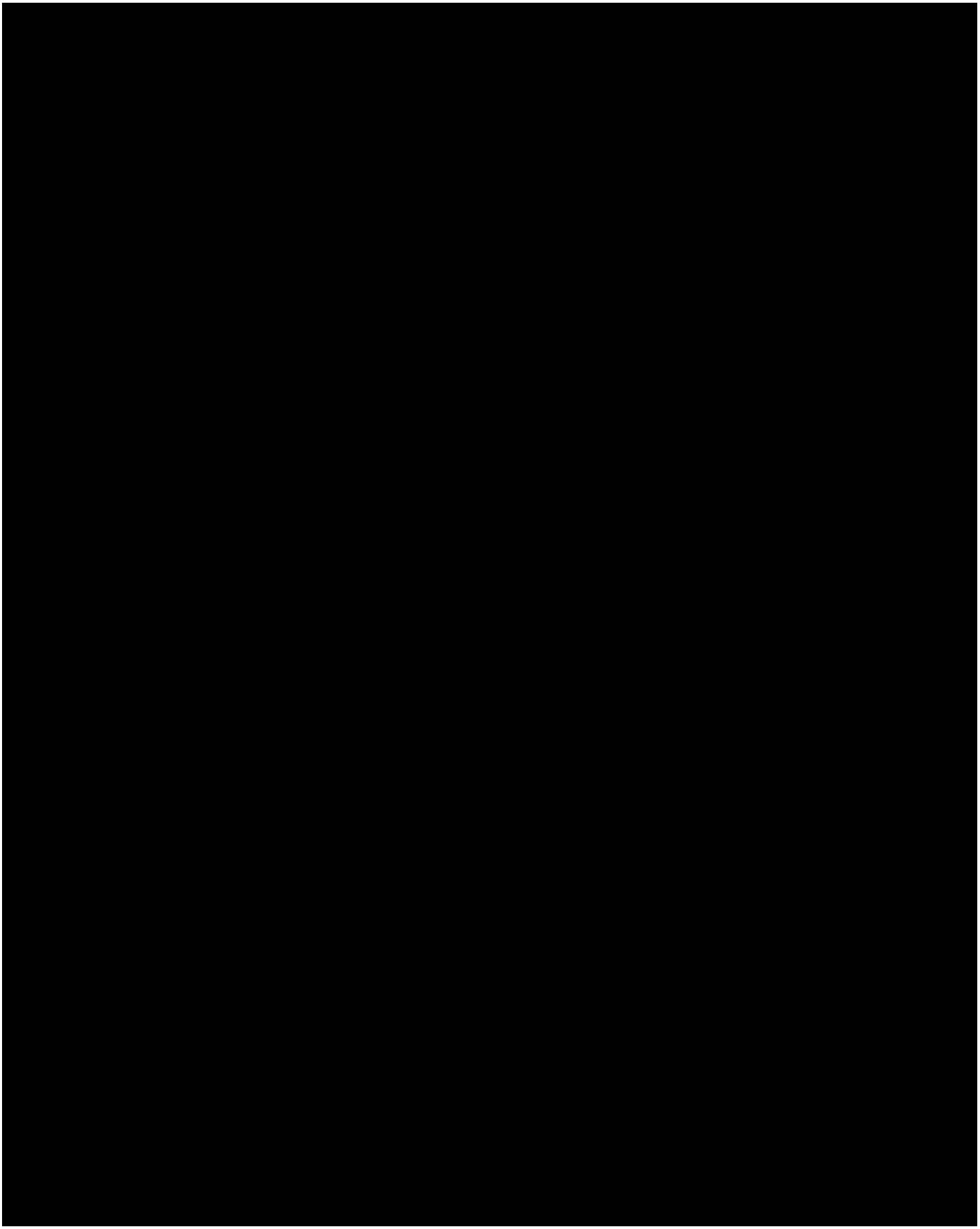
[redacted]

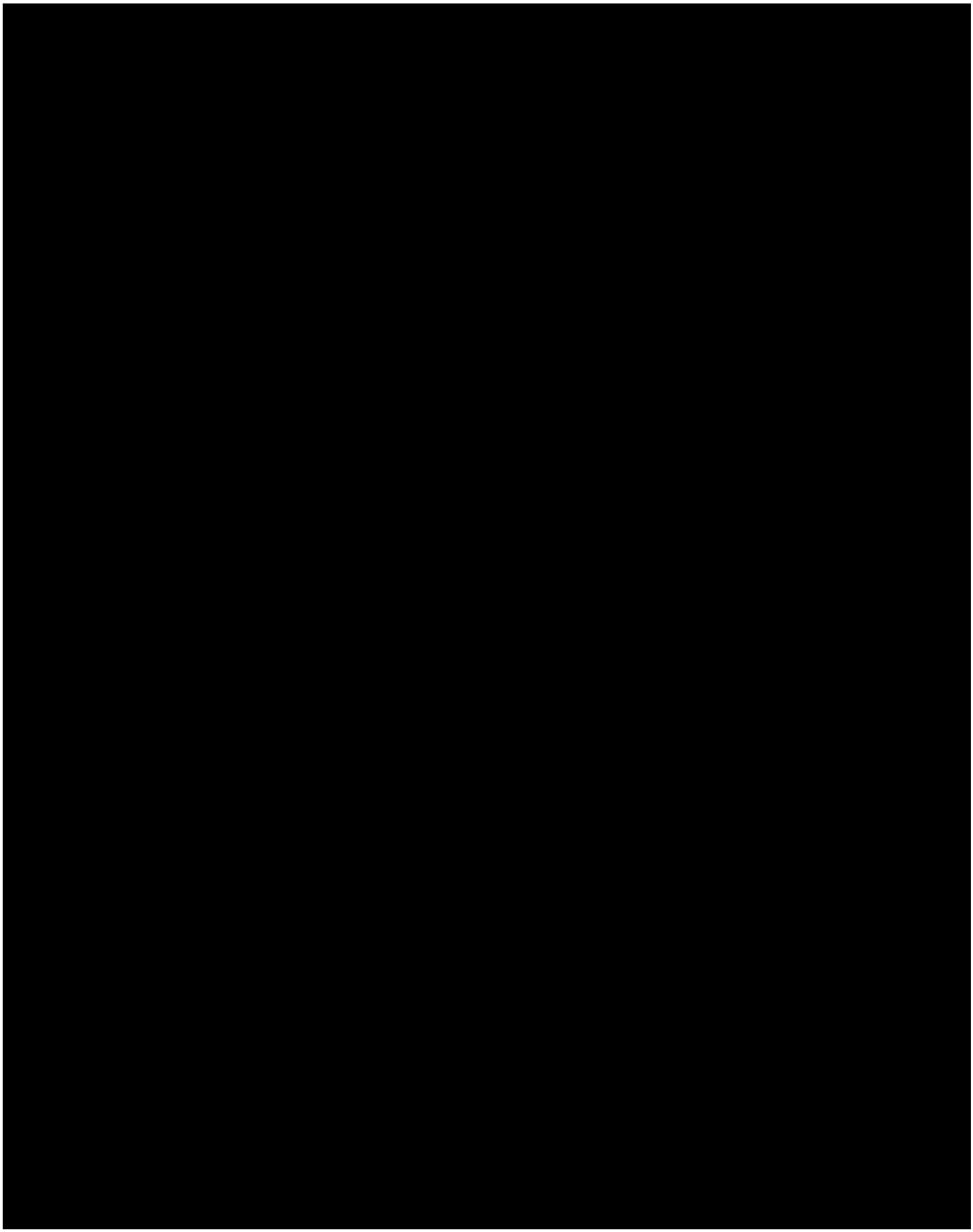


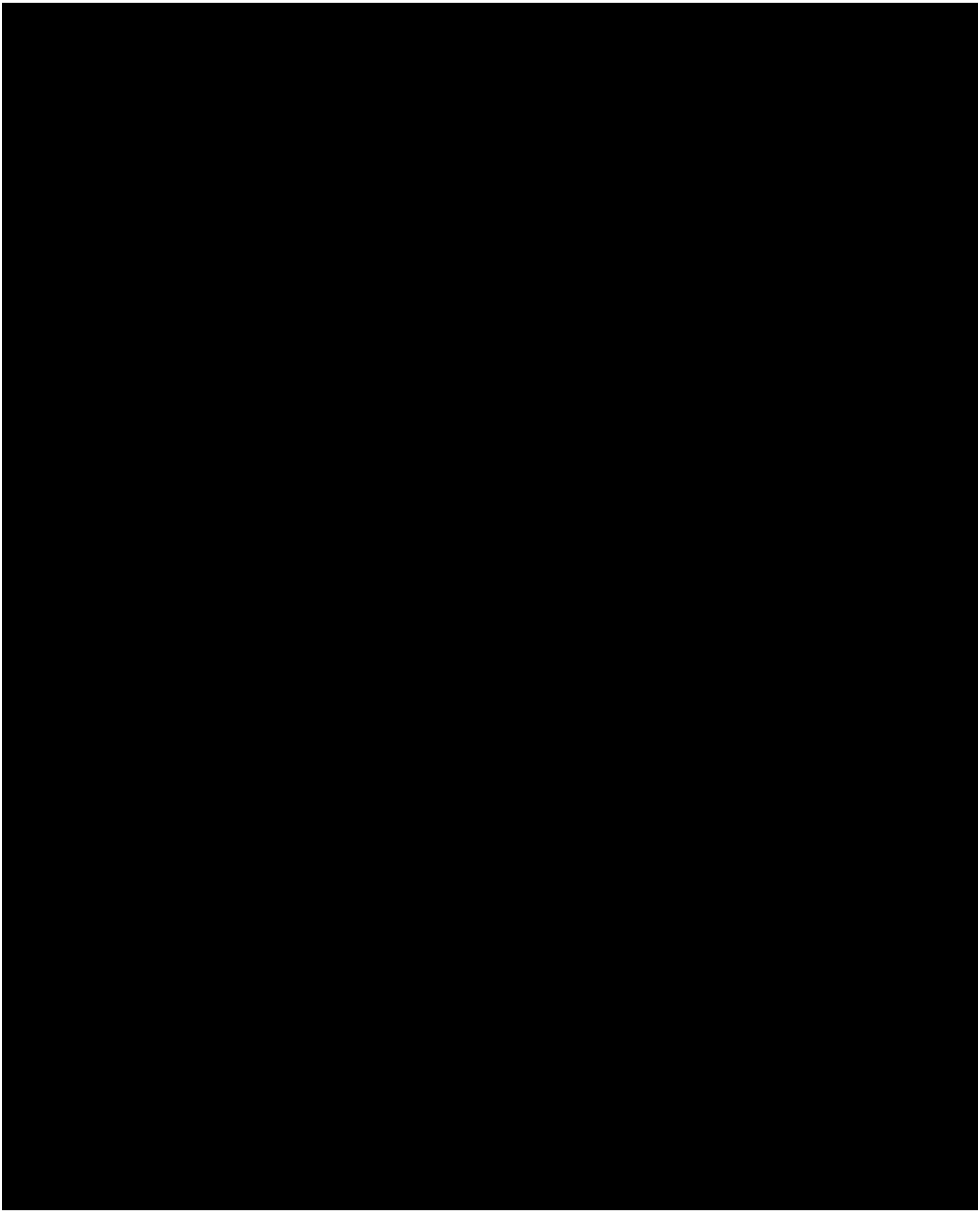












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