Clinical Trial Protocol

Protocol Title:	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
Study Phase:	2c
Investigational Product Name:	LNZ101 [redacted] and LNZ100 [redacted] Ophthalmic Solution
IND Number:	120,609
Indication:	Presbyopia
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:	14Jan2022
Amendment 1:	11Mar2022
Amendment 2:	23May2022
Amendment 3:	17Jun2022

Confidentiality Statement

MEDICAL MONITOR

Medical Monitor:	[redacted]

ORA PERSONNEL

Department Vice President:	[redacted]
Project Manager:	[redacted]

SYNOPSIS

Protocol Title:	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
Investigational Product:	LNZ101 [redacted] and LNZ100 [redacted] Ophthalmic Solution
Study Phase:	2c
Primary Objective(s):	To evaluate the safety and efficacy of [redacted] (LNZ101) compared with [redacted] (LNZ100) and vehicle in the treatment of Presbyopia.
Secondary Objective(s):	Not applicable
Overall Study Design	
Structure:	Multicenter, double-masked, randomized, crossover, active and vehicle-controlled, safety and efficacy study
Duration:	Approximately 3 weeks (4 Study Visits)
Controls:	Vehicle Ophthalmic Solution
Dosage/Dose Regimen/ Instillation/Application/ Use:	[redacted] One treatment will be administered bilaterally. [redacted] All subjects will receive each treatment once (crossover study design). Qualified subjects will be randomized at Visit 1 to one of three latin square design sequences detailing the order in which treatments will be administered over the three study visits. • [redacted] (LNZ101) dosed [redacted] bilaterally described above

- [redacted] (LNZ100) dosed [redacted] bilaterally described above
- Vehicle (non-preserved) ophthalmic solution dosed [redacted] bilaterally described above

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.

Number of Subjects:

Approximately 60 subjects will be enrolled [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 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 study visits;
3. Be 45-75 years of age of either sex and any race or ethnicity at Visit 1;

[redacted]

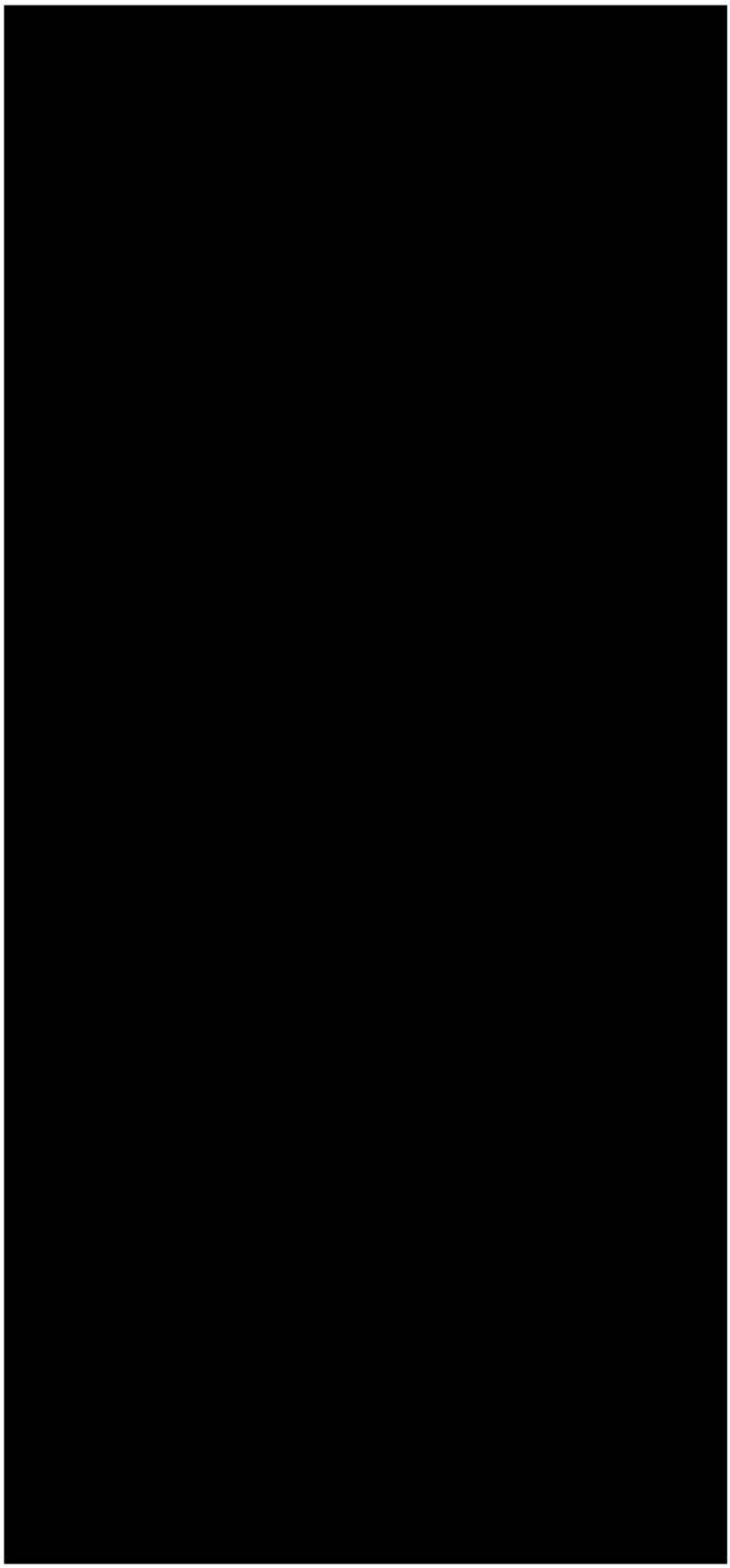
[redacted]

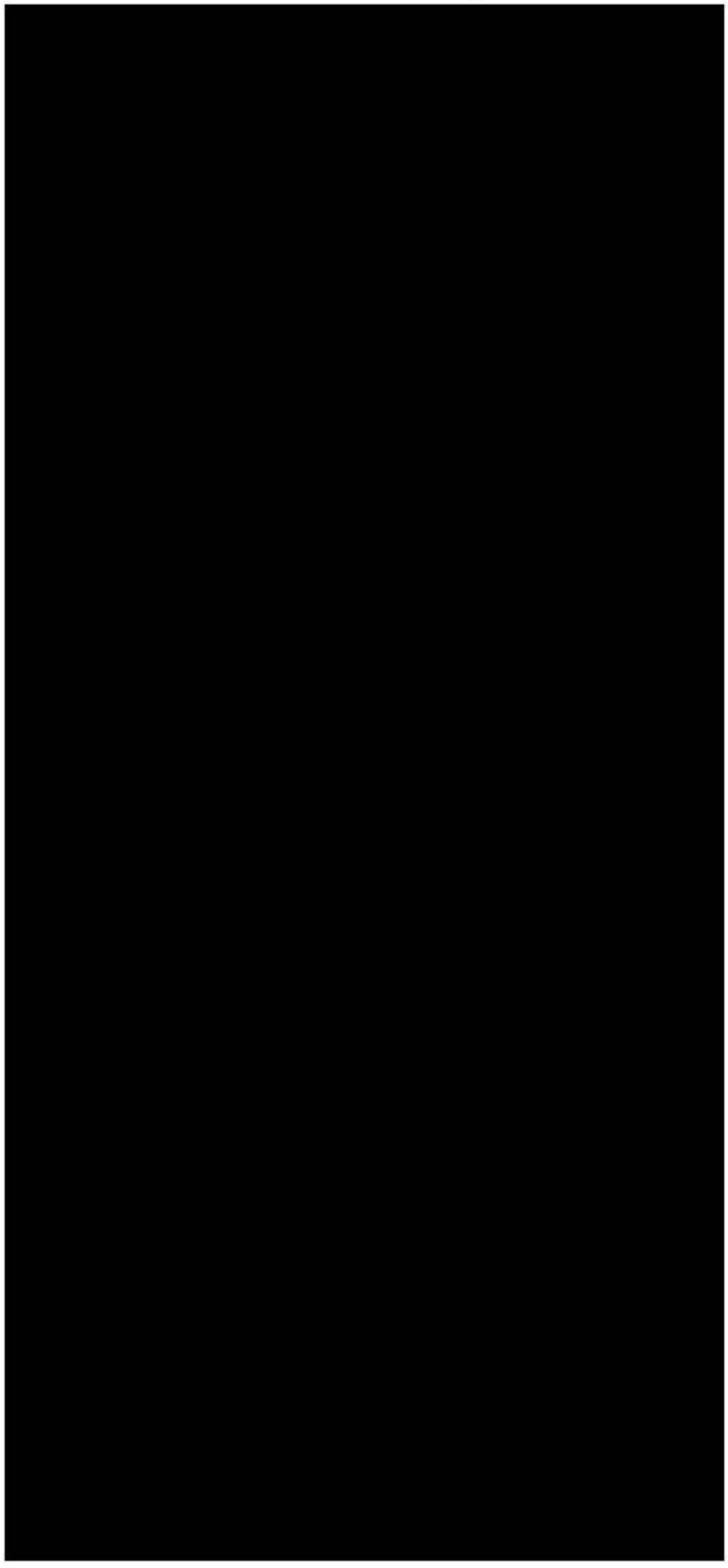
Exclusion Criteria:

Subjects must NOT:

1. Be a female of childbearing potential who is currently pregnant, nursing or planning a pregnancy;
2. Have known contraindications or sensitivity to the use of any of the study medications(s) or their components;
3. Have an active ocular infection at Visit 1 (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) in either eye;
4. Have moderate or severe dry eye [redacted] in either eye at Visit 1;
5. Have clinically significant abnormal lens findings (e.g., cataract) including early lens changes and/or any evidence of a media opacity in either eye during dilated slit-lamp biomicroscopy and fundus exam documented within 3 months of Visit 1 or at Visit 1;

[redacted]





Study Treatments:

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

Evaluation Criteria:

Efficacy Measures:

Primary Efficacy Variable:

- Percentage of subjects who achieve a 3-line (15-letters) or greater improvement from pre-treatment [redacted] monocular BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4m) [redacted]

Secondary Efficacy Variable:

[redacted]

Exploratory Variables:

[redacted]

[redacted]

Safety Measures:

- Loss of BCDVA
- Low-luminance Best Corrected Distance Visual Acuity
- Slit-lamp biomicroscopy and fundoscopy
- Conjunctival redness [redacted]
- IOP [redacted]
- Adverse Events (reported, elicited, and observed)

Other Measures:

- Patient-reported outcome (PRO) questionnaire
- *NeurOptics*® VIP®-300 Light Adapted Pupillometry
- Monocular and binocular uncorrected distance Visual Acuity
- Drop instillation assessment

General Statistical Methods and Types of Analyses

General Considerations:

In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean, SD, median, min, and max). Qualitative/categorical data will be summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.10 significance level.

The study eye, defined in section 8.3.1, will be used for all monocular analyses. The fellow eye will inherently be included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The primary [redacted] efficacy analyses will be conducted in the modified intent-to-treat (mITT) population defined in section 10.2.1. The mITT population will be analyzed as treated and will be used for the primary and monocular secondary efficacy analyses.

For primary [redacted] endpoints, sensitivity analyses will be performed using the ITT population with observed data only. Additionally, analysis on the primary efficacy variable will be performed on the per protocol (PP) population defined as all subjects who complete the study without major protocol violations/deviations. The PP population will be analyzed as treated using observed data only.

[redacted]

Safety analyses will be conducted in the safety population defined as all randomized subjects who received treatment. The safety population will be analyzed as treated.

Sample Size:

This study is expected to complete at least 40 evaluable subjects in each treatment group within the mITT population. This sample size was informed with results from the previous Phase 2b study. 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 treatment groups. 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 best distance corrected VA at 40 cm (monocular assessment) while the vehicle group 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 group 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 arm have at least a 3-line improvement, assuming non-responder concordance is at least 60.5%. [redacted] It is estimated that the LNZ100 treatment will fall to a response rate around 12% at the later time points (7 hours or later). 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%.

Primary Efficacy 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 [redacted] monocular BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4m) [redacted]. Primary analysis will use the mITT population. The primary

analyses will separately compare the [redacted] (LNZ101) arm versus the vehicle arm, and the [redacted] (LNZ100) versus the vehicle arm. LNZ101 will also be compared against LNZ100 as a secondary analysis.

Descriptive statistics will be presented by treatment group. Testing of the percentage of subjects with at least a 3-line (15-letter) near vision improvement without a loss of ≥ 5 letters distance vision (ETDRS chart at 4m) from pre-dose will be completed accounting for the correlations between treatments and periods within a subject using a logistic (binomial error and logit link) model estimated by generalized estimating equation methods. Aspects of the model include:

- Response measure: indicator of whether the subject had at least a 3-line (15-letter) improvement from pre-dose in the monocular assessment of BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4m) in the study eye.
- Fixed effect explanatory measures: sequence, period, and treatment.
- Repeated measures correlation will be estimated with an unstructured variance-covariance matrix in the GEE model.

Standard errors and CIs (80 and 90%) will also be presented for each treatment group and the difference between treatment groups. Pairwise comparisons among treatment groups will also be made using McNemar's tests.

[redacted]

[redacted]

Other Analysis:

[redacted]

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.

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.

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[redacted]

LIST OF ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
AE	Adverse Event
BCDVA	Best-corrected distance visual acuity
cd/m^2	Candela per square meter
CFR	Code of Federal Regulations
CI	Confidence Interval
CST	Clinical Trial Suite
eCRF	Electronic Case Report Form
D	Diopter
EKG	Electrocardiogram
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOL	Intraocular Lens
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional/Independent Review Board
ITT	Intent To Treat
IOL	Intraocular Lens
LASEK	Laser-Assisted Sub-Epithelial Keratectomy
LASIK	Laser in Situ Keratomileusis
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MAX	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIN	Minimum
mmHg	Millimeters of Mercury
M&S	M&S Technologies, Inc.
NCS	Not Clinically Significant
OD	Right Eye
OS	Left Eye
OU	Both Eyes
OTC	Over The Counter
PCO	Posterior Capsular Opacification
PP	Per Protocol
PRK	Photorefractive Keratectomy

QD	Once Daily
RGP	Rigid Gas Permeable
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
VA	Visual Acuity

1 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% has been shown to be generally safe and effective. Notably, the concentrations of Aceclidine and Brimonidine in this study (Aceclidine 1.75% and Brimonidine 0.08%) are substantially lower than the concentrations of these agents that are in clinical use.

2 STUDY OBJECTIVES

The objective of the study is to evaluate the safety and effectiveness of LNZ101 [redacted] and LNZ100 [redacted] ophthalmic solutions compared to vehicle in the treatment of presbyopia.

3 CLINICAL 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.

4 OVERALL STUDY DESIGN

This is a 4-visit 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] subjects will be randomly assigned to receive one of the following treatments:

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

Qualified subjects will be randomized at Visit 1 for which treatment will be administered at each study visit. One of the three treatments will be administered [redacted]. All subjects will receive each treatment once (crossover study design).

4.1 Study Eye Definition

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 best-corrected distance VA (BCDVA) at 40cm. If both eyes have the same VA at 40cm, 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.

Static Study Eye: The Static Study Eye is determined by the investigator (or designee) at Visit 1.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 60 subjects will be enrolled into [redacted] in order to complete at least 40 evaluable subjects in each treatment group within the mITT population.:

[redacted]

5.2 Study Population Characteristics

Healthy adult subjects between 45 and 75 years of age with presbyopia who do not have any conditions, in the Investigator's opinion, which may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation.

5.3 Inclusion Criteria

Subjects MUST:

1. Be able and willing to provide written informed consent and sign 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 study visits;
3. Be 45-75 years of age of either sex and any race or ethnicity at Visit 1;

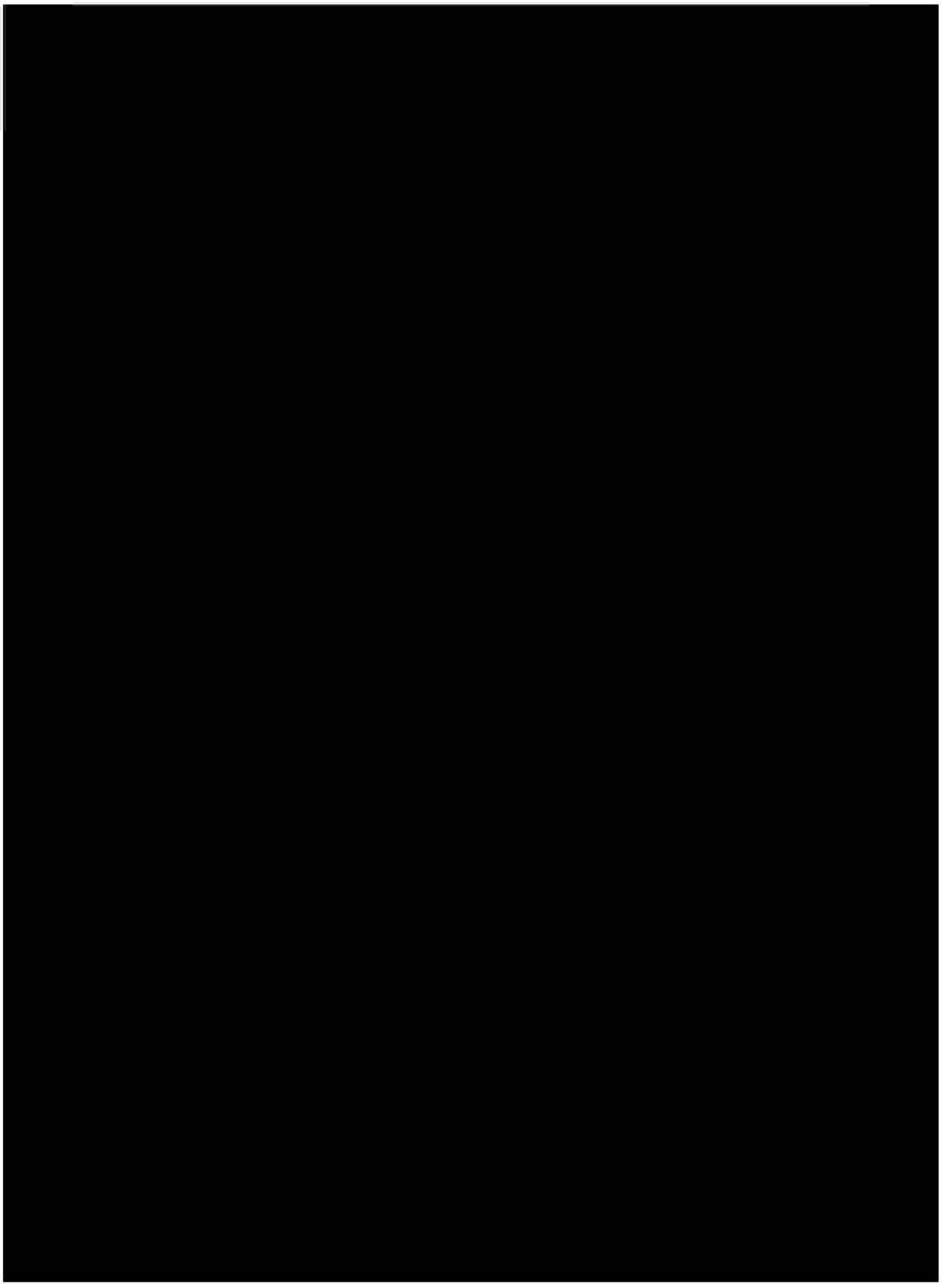
[redacted]

[redacted]

5.4 Exclusion Criteria

Subjects must NOT:

1. Be a female of childbearing potential who is currently pregnant, nursing or planning a pregnancy;
2. Have known contraindications or sensitivity to the use of any of the study medications(s) or their components;
3. Have an active ocular infection at Visit 1 (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) in either eye;
4. [redacted]



[redacted]

5.5 Withdrawal Criteria (if applicable)

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

1. Be a female of childbearing potential who is currently pregnant, nursing or planning a pregnancy; tests positive to a urine pregnancy test at Visit 2, 3 or 4; or refuses to use an adequate method of contraception for the duration of the study;

2. Have an active ocular infection at Visit 2, 3 or 4 (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) in either eye.

Subjects may also be withdrawn from the study for the following reasons:

- AE
- Lost to follow-up
- Withdrawal of consent by subject
- Investigator discretion
- Death
- Subject not following required study procedures
- Study terminated by the Sponsor
- Other

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

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Variable

- Percentage of subjects who achieve a 3-line (15-letters) or greater improvement from pre-treatment [redacted]

[redacted] BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4m) [redacted]

[redacted]

6.1.5 Criteria for Effectiveness

Changes in BCDVA at near distance will be calculated as the difference, in logMAR units, between the post-treatment monocular (study eye) and binocular BCDVA measurements at near (40 cm [redacted] minus the pre-

treatment monocular (study eye) and binocular BDCVA measurements at near (40 cm [redacted]). A 3-line improvement and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4m) is considered clinically meaningful.

6.2 Safety Measures

- Loss of BCDVA
- Low-luminance Best Corrected Distance Visual Acuity
- Slit-lamp biomicroscopy and fundoscopy
- Conjunctival Hyperemia [redacted]
- IOP [redacted]
- AEs (reported, elicited, and observed)

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment(s)/ Formulation(s)

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 arm 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.

7.1.2 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).

- The treatment will be administered by a separate, masked trained study technician [redacted]

[redacted] for LNZ101, LNZ100, and vehicle. If the drop is not properly instilled in each eye (e.g., subject blinks during instillation), the technician will administer another drop to ensure each drop is properly instilled. The same treatment should be administered to both eyes.

- A new clinical kit will be assigned to each subject.
- Both the technician who administers the treatment and the subject will be masked to the treatment identity.

7.2 Other Study Supplies

- Clarity HCG (RAC Medical Boca Raton, FL) will be used for pregnancy tests
- Fluorescein sodium ophthalmic strips, USP
- [redacted]

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in Section 5.2, 5.3, and 5.4 will be considered for entry into this study.

If a subject qualifies Visit 1 entry criteria but is unable to be scheduled for Visit 2 due to scheduling conflict, the subject may be re-screened an additional time. Re-screened subjects should retain their original screening number.

8.1.2 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.

8.1.3 Washout Intervals

[redacted]

[redacted]

8.2 **Concurrent Therapies**

The use of any concurrent medication, prescription or over-the-counter taken within 30 days of the study visit, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

All 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.

8.2.1 Prohibited Medications/Treatments

Washout intervals as described in Section 8.1.3 should be followed for all prohibited medications. 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.

8.2.2 Escape Medications

Not applicable

8.2.3 Special Diet or Activities

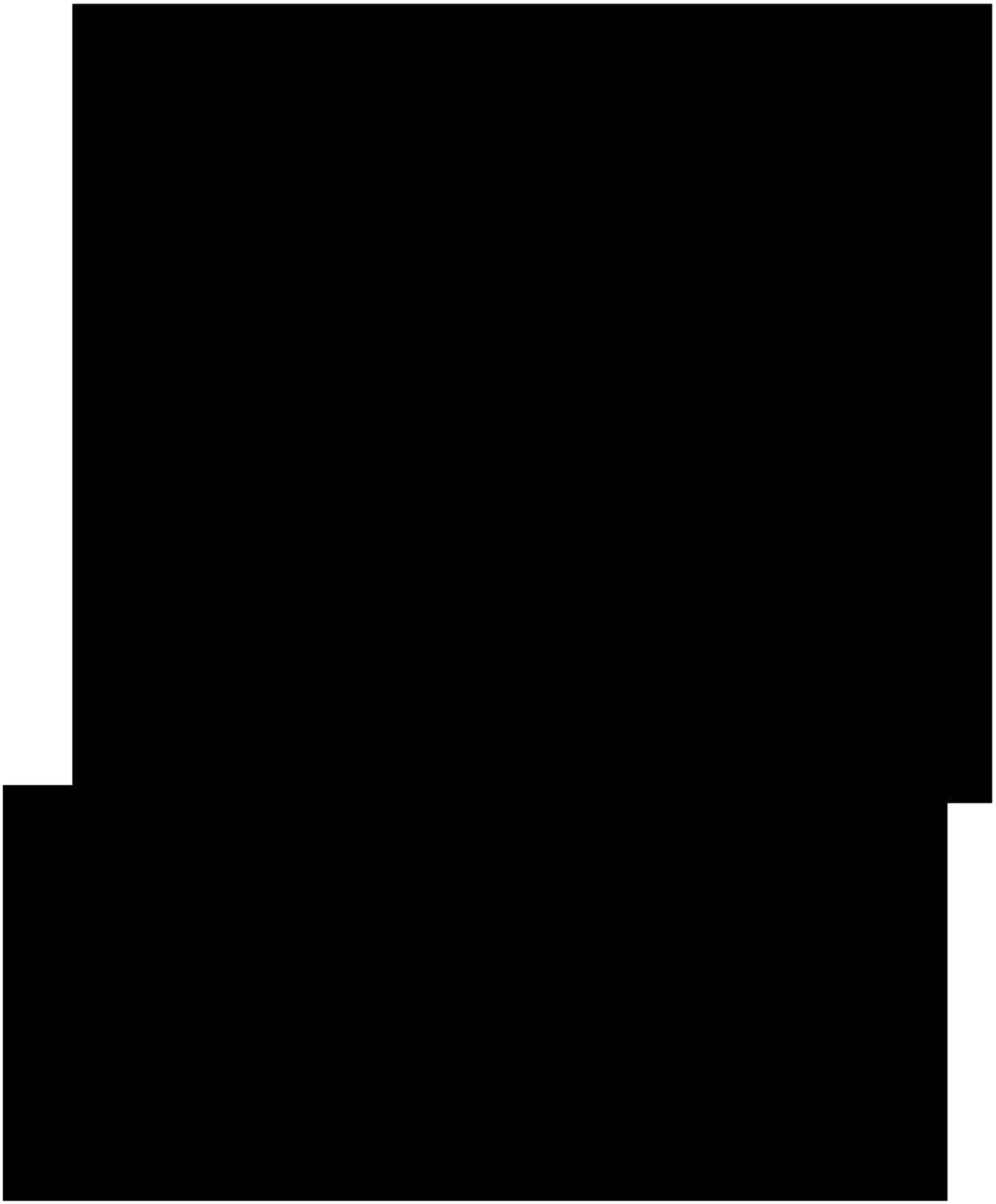
Not applicable

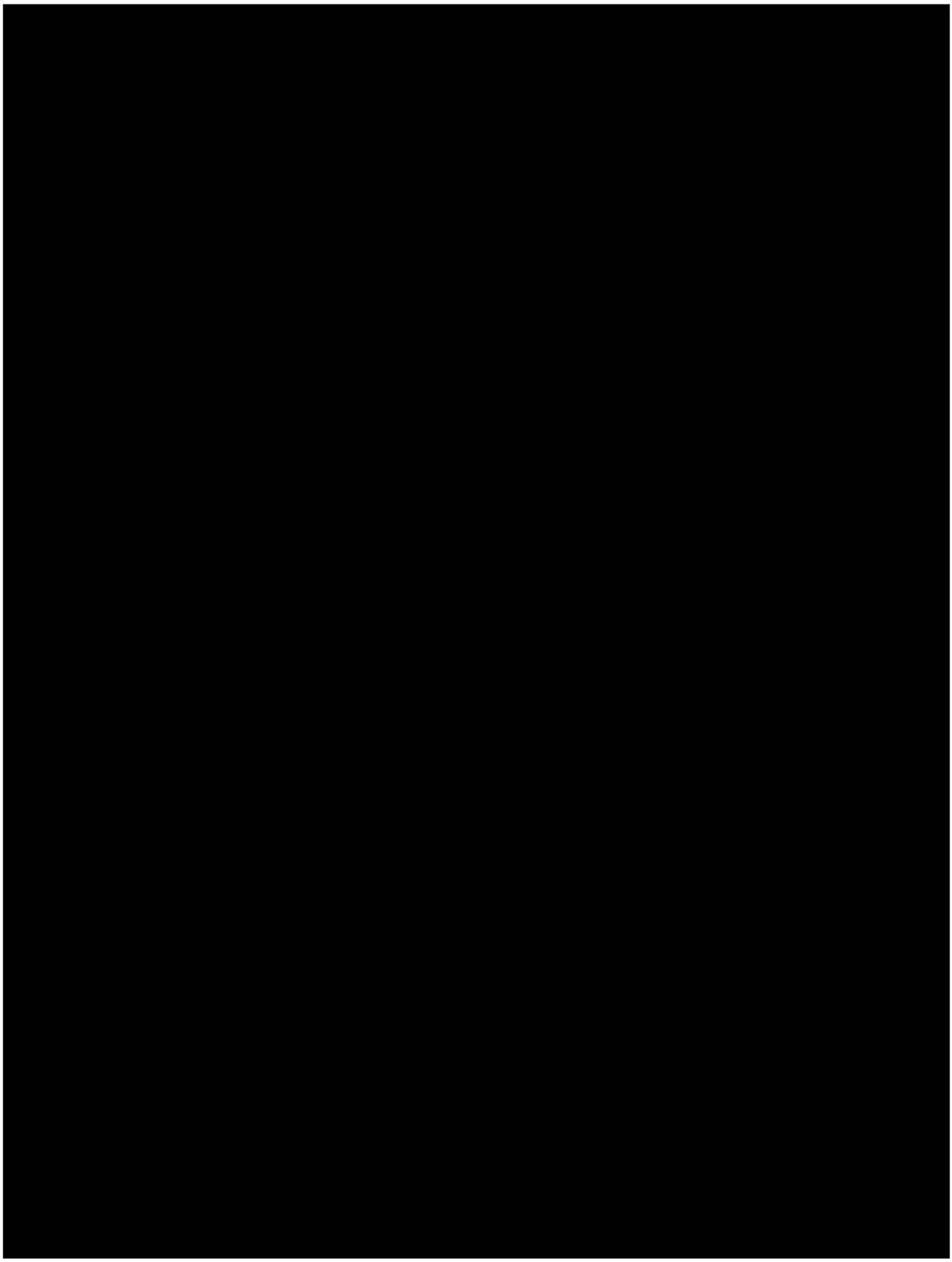
8.3 Examination Procedures

8.3.1 Procedures to be performed at the Study Visit in order listed below

Examinations will follow the below order within each visit:

[redacted]





8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visit

Refer to Appendix 1 for a schedule of measurements at the Visit.

8.4.2 Unscheduled Visits

In the case of an AE, an Unscheduled Visit may be performed by the Investigator. Unscheduled Visit assessments can include any of the following:

- Medical/medication history
- Urine pregnancy test
- VA assessments
- Slit-lamp biomicroscopy
- Conjunctival redness
- IOP
- Fluorescein staining
- AE query

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

8.5 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 Harmonisation (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 Title 21, parts 11, 50, 54, 56 and 312, as appropriate.

8.6 Subject Disposition

8.6.1 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).

8.6.2 Screen failed Subjects

Screened subject who does not meet the inclusion/exclusion criteria at any time prior to randomization at Visit 1.

8.6.3 Randomized Subjects

Subject who has signed the ICF, been issued a unique 4-digit subject number and has been randomized ot receive investigational product at Visit 1. Once randomized, the subject is enrolled in the study.

8.6.4 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 9.

8.6.5 Completed Subjects

Randomized subject who completes all scheduled study procedures through and including [redacted]

8.6.6 Withdrawn Subjects

A subject may be withdrawn for meeting any of the withdrawal criteria as described in Section 5.5.

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 9.

8.7 Study Termination

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

8.8 Study Duration

This study is comprised of 4 visits over a total duration of approximately 3 weeks.

8.9 Monitoring and Quality Assurance

During the course of the study an Ora, Inc. monitor, or designee, will make routine site visits to review protocol compliance, assess study drug 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, Ora, Inc. quality assurance and/or its designees, and the study sponsor may carry out on-site inspections and/or audits which 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.

9 ADVERSE EVENTS

9.1 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:

[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 investigational product (IP) in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, without any judgment about causality. An AE can arise from any use of the investigational product (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. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, patient characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release) associated with a medical device.

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 investigational product, 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 informed consent form through the subject's study exit visit.

9.1.1 Severity

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 investigational product 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.

9.1.2 Relationship to Investigational Product

The relationship of each AE to the investigational product should be determined by the Investigator using these explanations:

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

Suspected adverse reaction means any AE for which there is a reasonable possibility that the investigational product caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE. Types of evidence that would suggest a causal relationship between the investigational product and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with investigational product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with investigational product exposure, but is otherwise uncommon in the population exposed to the investigational product (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 investigational product-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an AE should be 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.

Adverse events 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, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events (SAE)

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 less than 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: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's

eyes (e.g., 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.

9.3 **Procedures for Reporting Adverse Events**

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

9.3.1 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/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the investigational product, 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 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 investigational product; and inform the IRB of the AE within their guidelines for reporting SAEs.

9.4 Procedures for Unmasking (if applicable)

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

9.5 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 (e.g. resolution, change in condition, or new treatment), a new Serious Adverse Event Report Form must be completed and faxed to Ora and/or the study sponsor within 24 hours. The original SAE Report Form is not to be altered. The Report Form should describe whether the event has resolved or continues and how the event was treated.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 General Considerations

All quantitative/continuous study assessments will be summarized by treatment (or treatment sequence) and visit and time point (as applicable) using descriptive

statistics (n, mean, SD, median, minimum, and maximum. All qualitative/categorical study assessments will be summarized by treatment (or treatment sequence), visits, and time point (as applicable) using frequency counts and percentages.

Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.10 significance level. When applicable, two-sided 80% and 90% Cis will be reported. All p-values (*P*) will be displayed to four decimal places, with *P* less than 0.0001 presented as '< 0.0001' and *P* greater than 0.9999 presented as '> 0.9999'.

[redacted]

All study data will be listed by subject, treatment, and time point (as applicable).

At each visit, the study eye, defined in Section 4.1, will be used for all monocular analyses. The fellow eye will be inherently included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The primary [redacted] analyses will be conducted in the modified intent-to-treat (mITT) population. The mITT population is defined in Section 10.2.1. The mITT population will be analyzed as treated and will be used for the primary [redacted] efficacy analyses. For primary [redacted] analyses, sensitivity analyses will be conducted as follows: if subjects do not meet the mITT criteria at any given visit, their improvement indicator (success or failure) at that visit will be imputed once as failure and once as success thereby testing/validating the implicit generalized estimating equation (GEE) imputation.

Sensitivity analyses on the primary efficacy variable will be performed using the ITT population with observed data only to assess robustness of the results from the mITT population. Additionally, analysis on the primary efficacy variable will be performed on the per protocol (PP) population defined as all subjects who complete the study without major protocol violations/deviations. The PP population will be analyzed as treated using observed data only.

Primary [redacted] efficacy endpoints will be analyzed for all available data as treated.

Safety analyses will be conducted in the safety population defined as all randomized subjects who received treatment. The safety population will be analyzed as treated. If a subject receives a particular treatment on more than 1 visit, data from both visits will be used in the safety analyses. Data from both visits will be averaged for continuous data and worse value will be used for categorical data.

10.2 Study Populations

10.2.1 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population consists of the study eye with baseline monocular BCDVA at 40 cm meeting the logMAR requirements listed in inclusion criteria in Section 5.3, exclusion criteria in Section 5.4 [redacted] who are randomized. The mITT population will be analyzed as treated and will be the primary population used for the primary [redacted] efficacy analyses. [redacted].

Pairwise comparisons between treatment groups and changes from pre-treatment will use the mITT population using only those eyes which have baseline/pre-treatment monocular [redacted] at the respective treatment visits. 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.

10.2.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of the study eye with monocular BCDVA at 40 cm meeting the logMAR requirements listed in inclusion criteria in Section 5.3 at each visit. 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 [redacted] efficacy endpoints. [redacted]

10.2.3 Per Protocol Population

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 using observed data only for confirmatory and sensitivity analyses.

10.2.4 Safety Population

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.

10.3 General Imputation Methods

As sensitivity analyses of the primary endpoint, missing data will be imputed as failures in the study eyes which do not meet the mITT criteria at either 1 or both treatments in the pairwise treatment comparisons. A similar imputation will be done

imputing missing data (data not meeting the mITT criteria) as successes in the mITT GEE analysis. Additionally, analysis on the primary efficacy variable will be performed on the ITT and PP populations using observed data only.

10.4 **Primary Efficacy Variable**

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

[redacted]

10.8 **Sample Size**

This study is expected to complete at least 40 evaluable subjects in each treatment group 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 treatment groups. 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 best distance corrected VA (monocular assessment) while the vehicle group has 7.5% of subjects with a 3-line improvement, assuming the non-responder concordance is at least 52[redacted]%. With the same assumption on the vehicle group 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 arm have at least a 3-line improvement, assuming non-responder concordance is at least 60.5%.

[redacted]

10.9 **Demographic and Baseline Characteristics**

Subject demographics: gender, race, ethnicity, and iris color will be presented using discrete summary statistics. Age will also be presented using continuous summary statistics.

10.10 **Primary Efficacy Analyses**

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 [redacted] monocular BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4m) [redacted]. Primary analysis will use the mITT population. The primary analyses will separately compare the LNZ-101 arm versus the vehicle arm, and the LNZ100 arm versus the vehicle arm. [redacted]

Descriptive statistics will be presented by treatment group. Testing of the percentage of subjects with at least a 3-line (15-letter) improvement in the study eye from pre-

dose without a loss in BCDVA ≥ 5 letters (ETDRS chart at 4m) will be completed accounting for the correlations between treatments and periods within a subject using a logistic (binomial error and logit link) model estimated by generalized estimating equation methods. Aspects of the model include:

- Response measure: indicator of whether the subject had at least a 3-line (15-letter) improvement in the study eye from pre-dose in the monocular assessment of BCDVA at 40 cm and no loss in BCDVA ≥ 5 letters (ETDRS chart at 4m).

- Fixed effect explanatory measures: sequence, period, and treatment.

- Repeated measures correlation will be estimated with an unstructured variance-covariance matrix in the GEE model.

Standard errors and Cis (80 and 90%) will also be presented for each treatment group and the difference between treatment groups. Pairwise comparisons among treatment groups will also be made using McNemar's tests.

10.14 Adjustment 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 also be no adjustments for multiplicity for multiple treatment arms and multiple comparisons to vehicle.

10.15 Safety Analysis

The percentage of subjects with treatment-emergent adverse events (TEAEs) will be summarized for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Slit lamp biomicroscopy, IOP, conjunctival redness, best-corrected VA, low-luminance best-corrected VA will be summarized descriptively using quantitative and qualitative summary statistics as appropriate.

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

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of investigational products in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent 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. If the subject is under the legal age of consent, the

consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form 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/IEC 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 study sponsor and provided in writing by Ora and/or study sponsor prior to the consent process.

11.1.2 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/ERC approved version of the ICF will be used.

11.2 Ethical Conduct of the Study

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

11.3 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 in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the sponsor, the IRB/IEC approving this study, the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), 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 investigational product may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

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

11.4.1 Retention of Documentation

All study related correspondence, patient records, consent forms, record of the distribution and use of all investigational products and copies of case report forms should be maintained on file for at least two 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 investigational product. 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.

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

11.5.1 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 the 4-digit subject number and visit number listed on the kit.

The LNZ101 ophthalmic solution clinical kits will contain one sterile container of the combination product LNZ101. The LNZ100 ophthalmic solution clinical kits will contain one sterile container of the combination product LNZ100. The vehicle ophthalmic solution kits will contain one sterile container of vehicle ophthalmic solution. The final solutions to be administered to the study participants will be provided in identical sterile containers in order to mask the study treatment to the study drug administrator and the study subject.

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."

11.5.2 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.

11.5.3 Accountability of Investigational Product

The investigational product is to only be administered by a masked 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.

11.5.4 Return or Disposal of Investigational Product

All investigational products will be returned to the sponsor or their designee or destroyed. The return or disposal of investigational product will be specified in writing.

11.6 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.

11.7 **Handling of Biological Specimens**

Not applicable

11.8 **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.

12 REFERENCES

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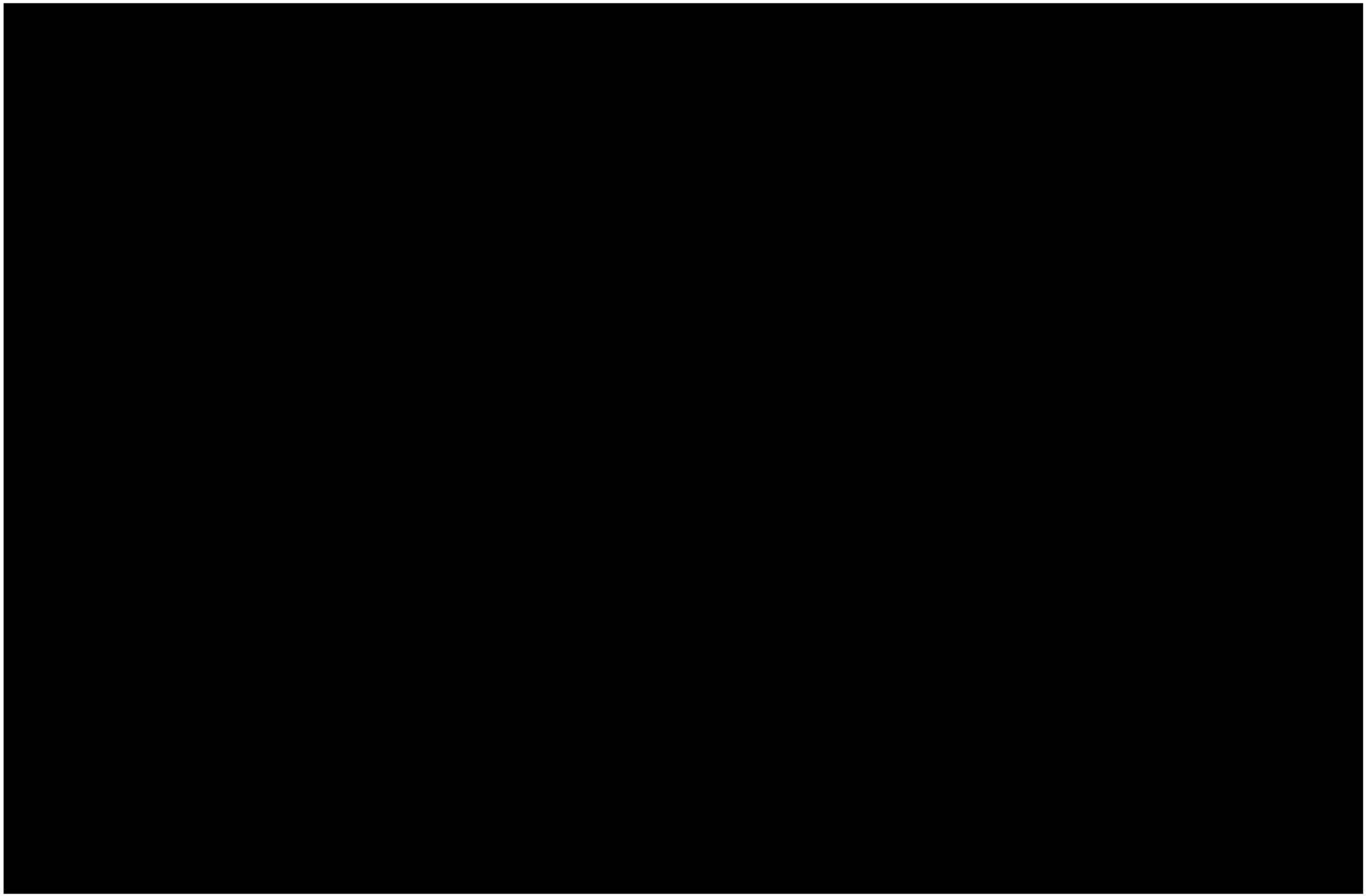

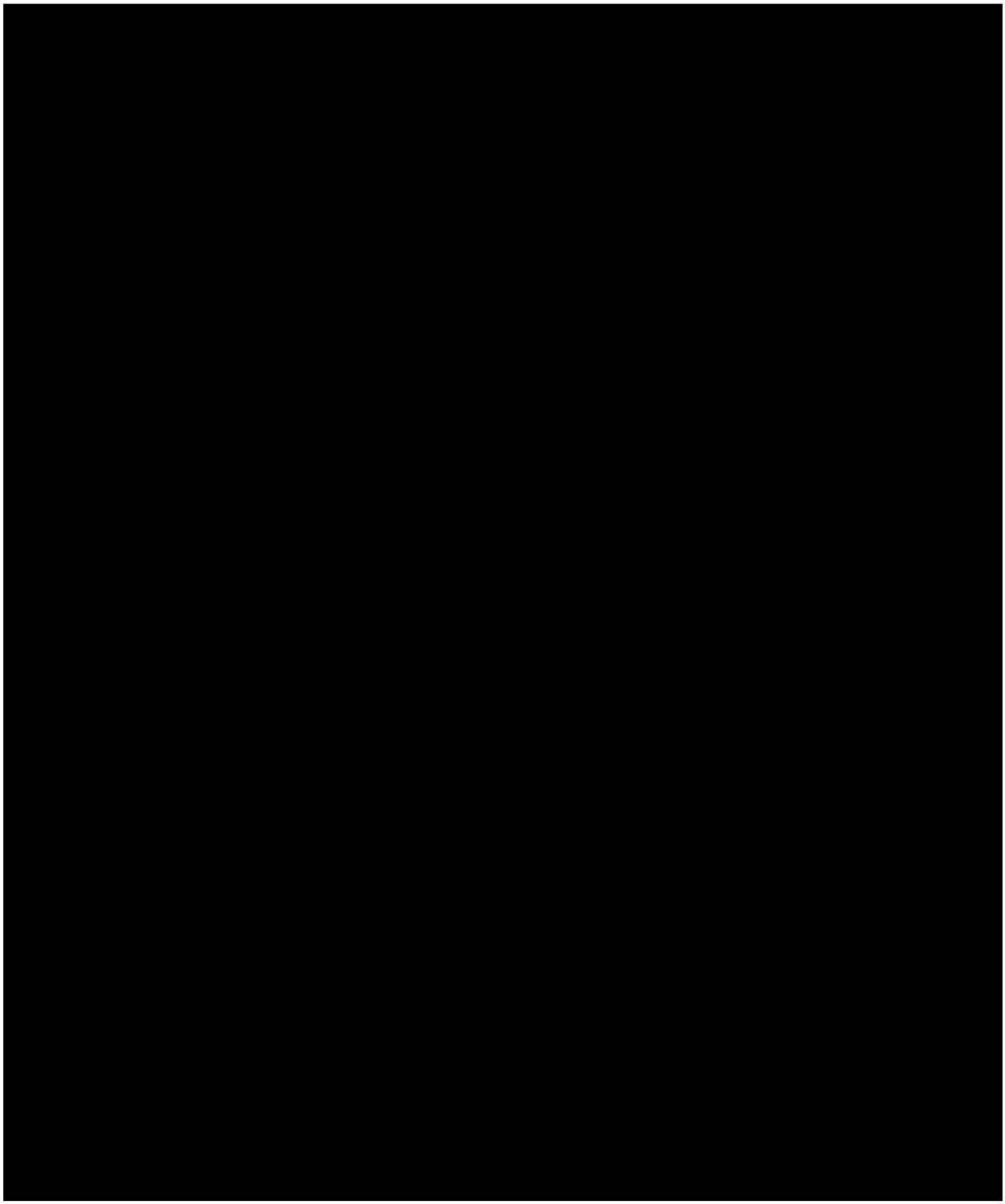

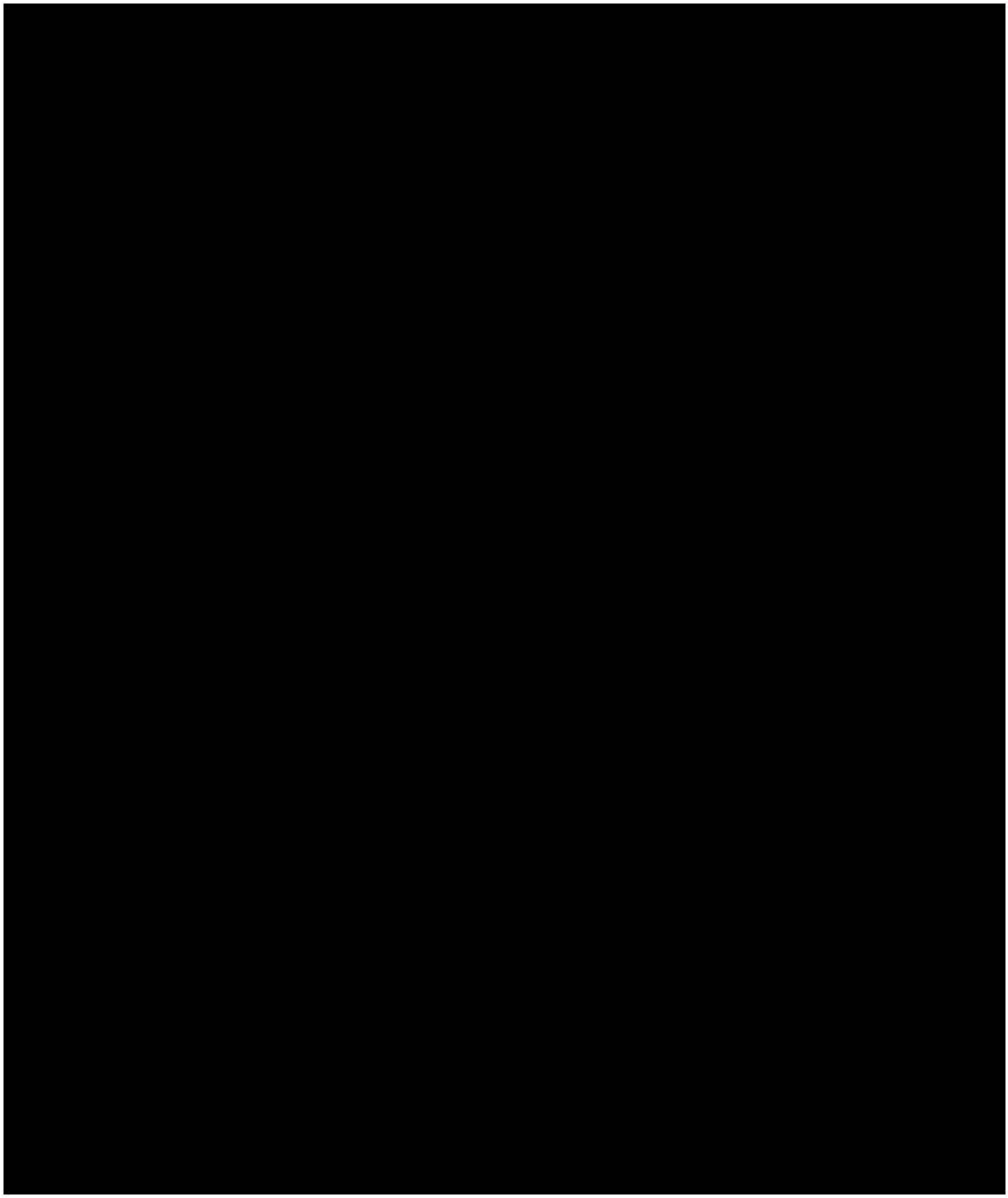

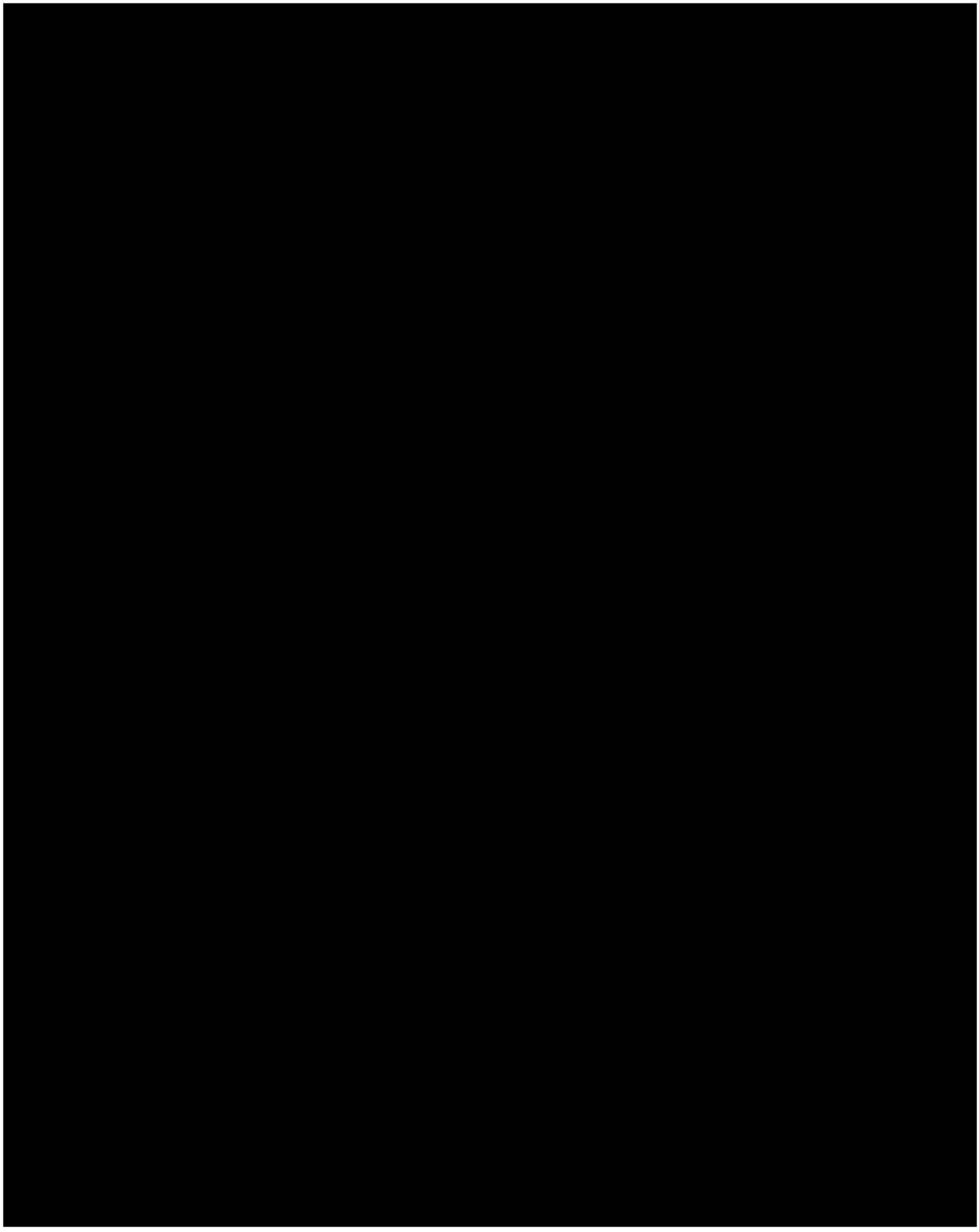

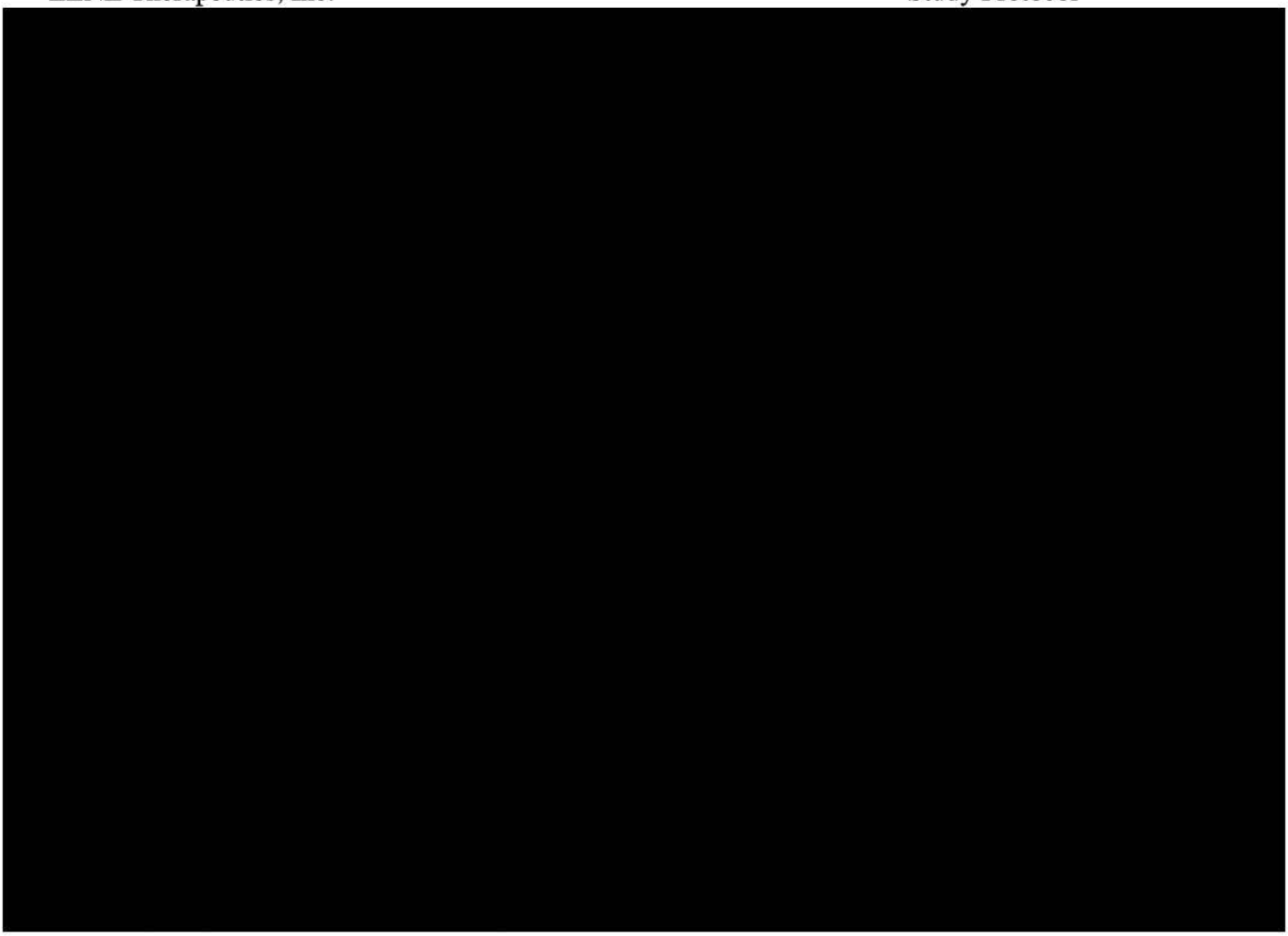

Appendix 4: Sponsor and Ora Approvals

Protocol Title:	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
Version and Date:	Amendment 3 (17Jun2022)

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

[redacted]

Appendix 5: Investigator's Signature

Protocol Title:	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
Version and Date:	Amendment 3 (17Jun2022)

I agree to implement and conduct the study diligently and in strict compliance with the protocol, Good Clinical Practices and all applicable laws and regulations. I agree to maintain all information supplied by Ora and the sponsor in confidence and, when this information is submitted to an institutional review board (IRB), ethical review committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

Principal Investigator