Clinical Trial Protocol 22-150-0017

Protocol Title:	A Multi-Center, Double-Masked Phase 3 Evaluation of the Long-Term Safety of LNZ101 in Presbyopic Subjects
Protocol Number:	22-150-0017
Study Phase:	Phase 3
Investigational Product Name:	[redacted]
IND/IDE/PMA Number:	120609
Indication:	Presbyopia
Investigators:	TBD
Sponsor:	LENZ Therapeutics [redacted]
Contract Research Organization:	[redacted]
IRB/IEC:	[redacted]

	Date
Original Protocol:	Version 1.0 (17Nov2022)
Amendment 1:	Version 2.0 (07Feb2023)
Amendment 2:	Version 3.0 (01May2023)
Amendment 3:	Version 4.0 (23Jun2023)
Amendment 4:	Version 5.0 (17Aug2023)

Confidentiality Statement

SPONSOR PERSONNEL

Sponsor:	LENZ Therapeutics, Inc. [redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

1.0 SYNOPSIS

Protocol Title:	A Multi-Center, Double-Masked Phase 3 Evaluation of the Long-Term Safety of LNZ101 in Presbyopic Subjects
Protocol Number:	22-150-0017
Investigational Products:	LNZ101 (Aceclidine 1.75%/Brimonidine 0.08%) Ophthalmic Solution LNZ100 (Aceclidine 1.75%) Ophthalmic Solution Vehicle Ophthalmic Solution
Study Phase:	Phase 3
Primary Objective:	To evaluate the long-term safety of LNZ101/LNZ100 compared with vehicle in presbyopic subjects
Secondary Objective:	Not applicable
Overall Study Design:	
Structure:	A multi-center, double-masked, randomized, placebo (vehicle)-controlled, safety study
Duration:	Approximately 28 Weeks
Controls:	Vehicle Ophthalmic Solution
Dosage/Dose Regimen/ Instillation/Application/Use:	Enrolled subjects will be randomized to receive LNZ101, LNZ100, or vehicle bilaterally once a day. Subjects will be instructed to dose 2 drops in both eyes (OU) (1 drop in each eye followed by 2 minutes later, another drop in each eye). Subjects will dose for approximately 26 weeks.
Summary of Visit Schedule:	• Visit 1 (Day -60 to Day -4): Screening • Visit 2 (Day 1, Baseline): Baseline Assessments & Enrollment • Visit 3 (Day 15 ± 2 days): Safety Assessments • Visit 4 (Day 43 ± 7 days): Safety Assessments • Visit 5 (Day 85 ± 7 Days): Safety Assessments

	• Visit 6 (Day 127 ± 7 Days): Safety Assessments • Visit 7 (Day 180 ± 14 Days) End of Study Visit/Early Termination (ET): Safety Assessments & Exit
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 andthe evaluation of clinical endpoints. Randomization will be at a 2:2:1 ratio (LNZ101:LNZ100:Vehicle).
Study Population Characteristics:	
Number of Subjects:	Approximately 350 subjects (140 LNZ101; 140 LNZ100; 70 vehicle) will be enrolled and treated for approximately 26 weeks.
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; 4. Be presbyopic in both eyes as determined by the Investigator and documented at Visit 1; 5. Have +1.00 to -4.00 diopters (D) of sphere (calculated in minus cylinder) with a spherical equivalent (SE) that is no more myopic than -4.00 D MRSE in both eyes determined by manifest refraction documented at Visit 1;

	6. Have ≤2.00 D of cylinder (minus cylinder) in both eyes determined by manifest refraction documented at Visit 1; 7. Have less than or equal to 0.20 logarithmic minimum angleof resolution (logMAR) (approximately 20/32 Snellen or better) best-corrected distance visual acuity (BCDVA) in each eye at Visit 1; 8. Have a negative urine pregnancy test at Visits 1 and 2, if female of childbearing potential (those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control isdefined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; 9. For pseudophakic subjects, intraocular lens (IOL) must be confirmed monofocal and with no significant posterior capsular opacification (PCO); Note: Subjects must also qualify based on all other IE criteria, including having a pre-IOL refraction and/or prescription that meets inclusion criteria #5 (refractive parameters for the study);
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 anyof 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 defined as corneal fluorescein staining superior, inferior, and central (combined) > 2 (Ora Calibra™ Scale) at Visit 1;[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;[2] 6. Neither eye can have intraocular pressure (IOP) that is less than 5 millimeters of mercury (mmHg) or greater than 22 mmHg documented at Visit 1, or have a prior diagnosis of ocular hypertension or glaucoma or currently being treated with any type of topical IOP lowering (glaucoma) medication at Visit 1; 7. Neither eye can have abnormal findings on dilated fundus exam documented within 3 months of Visit 1 or at Visit 1, or a known history of retinal detachment or clinically significant retinal disease;[2] 8. Neither eye can have a known history or diagnosis in the past of: iritis,scleritis, or uveitis, whether active or inactive; 9. Subject must not have had surgical intervention (ocular or systemic) within 6 months prior to Visit 1, or a planned surgical intervention during the study; 10. Subject must not have been dosed with investigational drug in LENZ study 22-150-0015, 22-150-0018, or 22-100-0007;

[1] For qualified subjects, Visit 1 data from study 22-150-0015 or 22-150-0018 can be used to meet this criterion if conducted within 60 days of 22-150-0017 Visit 1. Additionally, punctal plugs are acceptable if they have been in place for a minimum of 90 days prior to visit 1.
[2] For qualified subjects, Visit 1 data from study 22-150-0015 or 22-150-0018 can be used to meet this criterion if conducted within 60 days of 22-150-0017 Visit 1.

	11. Subject must not have been dosed with an investigational drug or participated in a device study within 1 month of Visit 1; 12. Subject must not have a diagnosis of diabetes mellitus or an elevatedblood sugar greater than 150mg/dl, or HbA1c of greater than or equal to 6.5% as measured within the past 3 months;[3] 13. Subject must not have a condition or a situation, which in the Investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation, including but not limited to unstable: cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease; 14. Neither eye can have undergone any prior retinal surgery, laser treatment or conventional surgery for retinal hole and retinal tears; 15. Subject must not have undergone prior LASIK or PRK surgery within 12 months of Visit 1: Subjects who have undergone LASIK or PRK more than 12 months prior to Visit 1 must qualify based on all other IE criteria, including having a pre-LASIK or pre-PRK prescription and/or refraction that meets Inclusion Criteria 5.
Study Formulations:	• LNZ101 (Aceclidine 1.75%/Brimonidine 0.08%) Ophthalmic Solution • LNZ100 (Aceclidine 1.75%) Ophthalmic Solution • Vehicle Ophthalmic Solution
Evaluation Criteria	
Safety Measures	1. Adverse events (AE) (reported, elicited,

[3] 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.

	and observed) 2. Vital signs (resting blood pressure and pulse) 3. Physical exam (general health, head, eyes, ears, nose, throat, and other comments) 4. Systemic labs (hematology, blood chemistry analysis, and urinalysis) 5. Pregnancy test 6. Monocular BCDVA at 4 m 7. Slit lamp biomicroscopy 8. IOP 9. Dilated fundus exams 10. Endothelial Cell Density (assessed via specular microscopy)

General Statistical Methods and Types of AnalysesAnalysis Sets

Safety Set – The Safety set will include all subjects who received at least 1 dose of the study drug.

Subjects in the safety set will be analyzed as treated.

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 performedat a 2-sided 0.05 significance level.

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

Safety analyses will be conducted in the safety set.

Sample Size

Approximately 350 subjects will be randomized into the study in a 2:2:1 ratio of LNZ101: LNZ100: vehicle (140 LNZ101; 140 LNZ100; 70 vehicle) completing dosing for approximately 26 weeks.

[redacted]

Safety Analysis

All safety data will be analyzed using the Safety set. Safety of LNZ101 and LNZ100 compared to vehicle 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 studydrug, will be summarized by treatment group using frequency and percent for each system organ class (SOC) andpreferred 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.

Changes from baseline in vital signs, physical examinations, systemic labs, monocular BCDVA, slit lamp biomicroscopy, IOP, dilated fundus examination and endothelial cell density will be summarized descriptively for at each visit by treatment group. Changes from baseline in endothelial cell density parameters will be tested between treatment groups using two-sample t-tests.

Full details of the safety analyses will be specified in the formal Statistical Analysis Plan.

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 (Aceclidine 1.75% and Brimonidine 0.08%) are substantially lower than the concentrations in common clinical use for both of these active ingredients.

TABLE OF CONTENTS

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
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
eCRF	Electronic case report form
D	Diopter
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full analysis set
FDA	Food and Drug Administration
GEE	Generalized estimating equation
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational new drug
IOL	Intraocular lens
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

[redacted]

Abbreviation	Definition
RGP	Rigid gas permeable
SAE	Serious adverse event
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% has been shown to be generally safe and effective. Notably, the concentrations of Aceclidine and Brimonidine in LNZ-101 formulation in this study (Aceclidine 1.75% and Brimonidine 0.08%) 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 of LNZ101/LNZ100 compared with placebo (vehicle) in presbyopic subjects.

4.0 CLINICAL HYPOTHESES

LNZ101 (Aceclidine 1.75%/Brimonidine 0.08% Ophthalmic Solution) and LNZ100 (Aceclidine 1.75%) have an acceptable safety profile when used in healthy adults with a history of presbyopia.

5.0 OVERALL STUDY DESIGN

This is a 7-visit, randomized, double-masked, multi-center, parallel-group study evaluating thesafety of LNZ101 and LNZ100 compared to vehicle in approximately 350 subjects with presbyopia.

Subjects will be in the study for approximately 28 weeks and will be seen at 7 study visits:

- Visit 1 (Day -60 to Day -4, Screening)
- Visit 2 (Day 1, Baseline)
- Visit 3 (Day 15 ± 2 days)
- Visit 4 (Day 43 ± 7 days)
- Visit 5 (Day 85 ± 7 days)
- Visit 6 (Day 127 ± 7 days)
- Visit 7 (Day 180 ± 14 days, End of Study Visit/Early Termination (ET))

Visit 1: Subjects will be screened through ophthalmic and safety assessments.

Visit 2: Subjects who remain qualified will be enrolled in this safety study and randomized 2:2:1 to receive LNZ101, LNZ100, or vehicle bilaterally. An ophthalmic technician will administer dose in office. Baseline ophthalmic safety assessments will be performed.

All subjects will be instructed to dose 2 drops in both eyes (OU) once daily (1 drop in each eye followed by 2 minutes later, another drop in each eye) at home. This regimen should be repeated each day.

Visit 3: Ophthalmic safety assessments will be repeated at Visit 3.

Visit 4: Ophthalmic safety assessments will be repeated at Visit 4.

Visit 5: Ophthalmic safety assessments will be repeated at Visit 5.

Visit 6: Ophthalmic safety assessments will be repeated at Visit 6.

Visit 7/End of Study Visit/Early Termination (ET)**:** Ophthalmic safety assessments will be repeated at Visit 7. Subjects will exit the study.

6.0 STUDY POPULATION

Approximately 350 healthy adult subjects from 45 to 75 years of age 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 allstudy visits;
3. Be 45-75 years of age of either sex and any race or ethnicity atVisit 1;
4. Be presbyopic in both eyes as determined by the Investigator and documented at Visit 1;
5. Have +1.00 to -4.00 diopters (D) of sphere (calculated in minus cylinder) with a spherical equivalent (SE) that is no more myopic than -4.00 D MRSE in both eyes determined by manifest refraction documented at Visit 1;
6. Have ≤2.00 D of cylinder (minus cylinder) in both eyes determined by manifest refraction documented at Visit 1;
7. Have less than or equal to 0.20 logarithmic minimum angleof resolution (logMAR) (approximately 20/32 Snellen or better) best-corrected distance visual acuity (BCDVA) in each eye at Visit 1;
8. Have a negative urine pregnancy test at Visits 1 and 2, if female of childbearing potential (those who have experienced menarcheand who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal[12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control isdefined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control;
9. For pseudophakic subjects, intraocular lens (IOL) must be confirmed monofocal and with no significant posterior capsular opacification (PCO);

   Note: Subjects must also qualify based on all other IE criteria, including having a pre-IOL refraction and/or prescription that meets inclusion criteria #5 (refractive parameters for the study);

6.2 Exclusion Criteria

1. Subject must not be a female of childbearing potential who is currently pregnant, nursing, or planning apregnancy;
2. Subject must not have known contraindications or sensitivity to the use of any of the study medications ortheir components;
3. Neither eye can have an active ocular infection at Visit 1 or at Visit 2 (bacterial, viral, or fungal), positive history ofan 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 defined as corneal fluorescein staining superior, inferior, and central (combined) > 2 (OraCalibra™ Scale) at Visit 1[4];
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 biomicroscopyand fundus exam documented within 3 months of Visit 1 or at Visit 1[5];
6. Neither eye can have intraocular pressure (IOP) that is less than 5 millimeters of mercury (mmHg) or greater than 22 mmHg documented at Visit 1, or have a prior diagnosis of ocular hypertension or glaucoma or currently being treated with any type of topical IOP lowering (glaucoma) medication at Visit 1;
7. Neither eye can have abnormal findings on dilated fundus exam documented within 3 months of Visit 1 or at Visit 1, or a known history of retinal detachment or clinically significant retinal disease[5];
8. Neither eye can have a known history or diagnosis in the past of: iritis, scleritis, or uveitis, whether activeor inactive;
9. Subject must not have had surgical intervention (ocular or systemic) within 6 months prior to Visit 1, or a planned surgical intervention during the study;
10. Subject must not have been dosed with investigational drug in LENZ study 22-150-0015, 22-150-0018, or 22-100-0007;
11. Subject must not have been dosed with an investigational drug or participated in a device study within 1 month of Visit 1;
12. Subject must not have a diagnosis of diabetes mellitus or an elevated blood sugar greater than 150mg/dl, or HbA1c of greater than or equal to 6.5% as measured within the past 3 months[6];
13. Subject must not have a condition or a situation, which in the Investigator's opinion, may put the subjectat increased risk, confound study data, or interfere significantly with the subject's studyparticipation, including but not limited to unstable: cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease;
14. Neither eye can have undergone any prior retinal surgery, laser treatment or conventional surgery for retinal hole and retinal tears;
15. Subject must not have undergone prior LASIK or PRK surgery within 12 months of Visit 1:

[4] For qualified subjects, Visit 1 data from study 22-150-0015 or 22-150-0018 can be used to meet this criterion if conducted within 60 days of 22-150-0017 Visit 1. Additionally, punctal plugs are acceptable if they have been in place for a minimum of 90 days prior to visit 1.

[5] For qualified subjects, Visit 1 data from study 22-150-0015 or 22-150-0018 can be used to meet this criterion if conducted within 60 days of 22-150-0017 Visit 1.

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

16. Subjects who have undergone LASIK or PRK more than 12 months prior to Visit 1 must qualify based on all other IE criteria, including having a pre-LASIK or pre-PRK prescription and/or refraction that meets Inclusion Criteria 5.

6.3 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 adequatemethod 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) at any visit in either eye.
- Subjects may also be withdrawn from the study for the following reasons:
  - Adverse event (AE)
  - Lost to follow-up
  - 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 Safety Endpoints

- Adverse events (AE) (reported, elicited, and observed)
- Pregnancy test
- Monocular BCDVA at 4 m
- Slit lamp biomicroscopy
- IOP
- Dilated fundus exams
- Endothelial Cell Density Assessments (assessed via specular microscopy)

8.0 STUDY MATERIALS

8.1 Study Treatments

8.1.1 Investigational Product

The study treatments are as follows:

- LNZ101 –Aceclidine 1.75% and Brimonidine 0.08% combination (non-preserved) Ophthalmic Solution
- LNZ100 – Aceclidine 1.75% (non-preserved) Ophthalmic Solution
- Vehicle ophthalmic solution

The two active ingredients (Aceclidine and Brimonidine) have been formulated and 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 kit number).

At Visit 2, the treatment will be administered by a trained study technician via instillation of two (2) drops bilaterally (OU), 1 drop in each eye followed by 2 minutes later, another drop in each eye. 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.

If the subject uses contact lens wear, the subject must wait at least 15 minutes after the second drop instillation to apply contact lens wear.

A total of 13 new kits will be assigned to each subject over the course of the study as follows:

Visit 2: 1 kit

Visit 3: 2 kits

Visit 4: 3 kits

Visit 5: 3 kits

Visit 6: 4 kits

Both the technician who administers the treatment and the subject will be masked to the treatment identity.

8.1.3 Subject Instructions

After randomization at Visit 2, subjects will receive IP and a dosing diary. Once dispensed to the subject, IP must be stored refrigerated at a temperature from 2-8ºC . Subjects will be instructed to save and return all unused IP and to bring their kits to all study visits. Subjects will also be instructed to record doses in their diary (paper). Subjects will exit the study after all assessments are complete at Visit 7.

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 intothis study.

Re-screening for any reason requires advanced discussion with and agreement by the Sponsor. Re-screened subjects should be assigned a new screening number.

9.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e. changes in a subject's medical treatment and/orstudy related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an informed consent form (ICF) and other written documentation in accordance with local privacy requirements (where applicable).

Additional information can be found in Section 12.1.1.

9.1.3 Washout Intervals

There are no washout intervals for this study.

9.1.4 Procedures for Final Study Entry

Subjects must satisfy all inclusion and none of the exclusion criteria in order to be entered into the study.

9.1.5 Pregnancy

Females must have a negative pregnancy test at Visits 1 and 2, if female of childbearing potential (those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as anadequate method of birth control.

In the event a female has a positive pregnancy test, the subject will be withdrawn from the study and the Investigator will notify [redacted] and the sponsor within 24 hours of knowledge of the event.

9.1.6 Methods for Assignment to Treatment Groups

Each subject who signs an ICF will be assigned a subject number (a six-digit number starting with the 3-digit site number followed by a sequential three-digit number starting with 001). Once a subject meets all qualification criteria at Visit 2, he/she will be randomized in a 2:2:1 ratio via an interactive response technology system to 1 of 3 treatment groups (1: LNZ101 or 2: LNZ100, or 3: vehicle). [redacted]

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

9.2 Concurrent Therapies and Medical History

The use of any concurrent medication, prescription, or OTC 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.

9.3 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:

9.3.1.1 Visit 1 (Day -60 to Day -4): Screening Visit

1. Informed consent / HIPAA
2. Demographic data
3. Medical and medication history
4. Inclusion and exclusion criteria review
5. Manifest refraction
6. Monocular BCDVA at 4 m
7. Konan Specular Microscopy to assess Endothelial Cell Density Assessments
8. Slit lamp biomicroscopy
9. Fluorescein staining*
10. IOP
11. Dilated indirect fundoscopy*
12. Vital signs (resting blood pressure and pulse)**
13. Physical examination (general health, head, eyes, ears, nose, throat, and other comments (HEENT)**
14. Systemic labs (hematology, blood chemistry analysis, and urinalysis) including urine pregnancy test (for females of child-bearing potential)**

15. End of visit AE query

    *Not required if conducted within previous 60 days as part of V1 for LENZ study 22-150-0015 or 22-150-0018

    **The order in which systemic labs, including urine pregnancy test, vital signs, and physical exam are collected during Visit 1 is up to the discretion of the Investigator

9.3.1.2 Visit 2 (Day 1) Baseline/Randomization

1. Medical and medication history update
2. AE query
3. Urine pregnancy test (for females of child-bearing potential)
4. Inclusion and exclusion criteria review including review of systemic laboratory results
5. Monocular BCDVA at 4 m
6. Slit lamp biomicroscopy
7. IOP
8. Undilated fundus exam
9. Randomization
10. Dispense IP
11. Instill IP

    Instillation of LNZ101 – 2 drops OU, LNZ100 – 2 drops OU, or Vehicle – 2 drops OU

    - Subjects will receive two drops bilaterally, 1 drop in each eye followed by 2 minutes later, another drop in each eye.

12. End of visit AE query
13. Provide Dosing Diary and dispensed IP kit

9.3.1.3 Visit 3 (Day 15 ± 2 days)

1. Collect IP kit(s) /Dosing Diary from previous visit
2. Medical and medication history update
3. AE query
4. Monocular BCDVA at 4 m
5. Slit lamp biomicroscopy
6. IOP
7. End of visit AE query
8. Provide Dosing Diary and dispense IP kits

9.3.1.4 Visit 4 (Day 43 ± 7 days)

1. Collect IP kit(s)/Dosing Diary from previous visit
2. Medical and medication history update
3. AE query
4. Vital signs (resting blood pressure and pulse)*
5. Physical examination (general health, head, eyes, ears, nose, throat, and other comments (HEENT)*
6. Systemic labs (hematology, blood chemistry analysis, and urinalysis)*
7. Monocular BCDVA at 4 m
8. Slit lamp biomicroscopy
9. IOP
10. End of visit AE query
11. Provide Dosing Diary and dispense IP kits

*The order in which systemic labs, including urine pregnancy test, vital signs, and physical exam are collected during Visit 4 is up to the discretion of the Investigator

9.3.1.5 Visit 5 (Day 85 ± 7 days)

1. Collect IP kit(s) /Dosing Diary from previous visit
2. Medical and medication history update
3. AE query
4. Vital signs (resting blood pressure and pulse)*
5. Physical examination (general health, head, eyes, ears, nose, throat, and other comments (HEENT)*
6. Systemic labs (hematology, blood chemistry analysis, and urinalysis)*
7. Monocular BCDVA at 4 m
8. Slit lamp biomicroscopy
9. IOP
10. End of visit AE query
11. Provide Dosing Diary and dispense IP kits

*The order in which systemic labs, including urine pregnancy test, vital signs, and physical exam are collected during Visit 5 is up to the discretion of the Investigator

9.3.1.6 Visit 6 (Day 127 ± 7 days)

1. Collect IP kit(s) /Dosing Diary from previous visit
2. Medical and medication history update
3. AE query
4. Monocular BCDVA at 4 m
5. Slit lamp biomicroscopy
6. IOP
7. End of visit AE query
8. Provide Dosing Diary and dispense IP kits

9.3.1.7 Visit 7 End of Study Visit/Early Termination (ET) (Day 180 ± 14 days)

1. Collect IP kit(s) /Dosing Diary from previous visit
2. Medical and medication history update
3. AE query
4. Vital signs (resting blood pressure and pulse)*
5. Physical examination (general health, head, eyes, ears, nose, throat, and other comments (HEENT)*
6. Systemic labs (hematology, blood chemistry analysis, and urinalysis) including urine pregnancy test (for females of child-bearing potential)*
7. Monocular BCDVA at 4 m
8. Konan Specular Microscopy to assess Endothelial Cell Density
9. Slit lamp biomicroscopy
10. IOP
11. Dilated indirect fundoscopy
12. End of visit AE query
13. Study Exit

*The order in which systemic labs, including urine pregnancy test, vital signs, and physical exam are collected during Visit 7 is up to the discretion of the Investigator

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

9.4 Schedule of Visits, Measurements and Dosing

9.4.1 Scheduled Visit

Refer to [redacted] for a schedule of measurements at each visit.

9.4.2 Unscheduled Visits

In the case of an AE, an unscheduled visit may occur. The investigator may perform additional assessments at their discretion. 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 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 (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 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 at Visit 7.

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 comprised of up to 7 visits over a total duration of approximately 28 weeks.

9.9 Monitoring and Quality Assurance

During the course of the study [redacted] 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 [redacted] quality assurance and/or its designees 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:

[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 theseexplanations:

- *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 aboutthe 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 notinclude 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 doesnot 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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] and the study sponsor with a complete case history, which includes a statement as to whether the event was orwas not suspected to be related to the use of the IP; and inform the IRB of the AE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

Medical Monitor:	[redacted]
Project Manager:	[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), [redacted] 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 [redacted] 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 (numberof 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 the first dose of study drug. Change from baseline will be calculated as follow-up measure minusbaseline measure.

Safety analyses will be conducted using the Safety set.

11.2 Analysis Sets

- Safety Set – The Safety set will include all subjects who have received at least 1 dose of the study drug. Subjects in the Safety set will be analyzed as treated.

11.3 Unit of Analysis

Both eyes will be displayed and analyzed for all ophthalmic safety variables.

11.4 Safety Endpoints

The safety endpoints are:

- AEs
- Vital signs (resting blood pressure and pulse)
- Physical exam (general health, head, eyes, ears, nose, throat, and other comments)
- Systemic labs (hematology, blood chemistry analysis, and urinalysis)
- Pregnancy test
- Monocular BCDVA
- Slit lamp biomicroscopy
- IOP
- Dilated fundus exams
- Endothelial Cell Density (assessed via specular microscopy)

11.5 Sample Size

Approximately 350 subjects will be randomized into the study in a 2:2:1 ratio of LNZ101: LNZ100: vehicle (140 LNZ101; 140 LNZ100; 70 vehicle) completing dosing for approximately 26 weeks.

A sample size of 100 subjects treated with LNZ101/LNZ100 will have at least 95% confidence of detecting adverse events that occur at a rate of 3% or greater.

11.6 Demographic and Baseline Characteristics

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

11.7 Safety Analysis

All safety data will be analyzed using the Safety set. Safety of LNZ101 and LNZ100 compared to vehicle 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.

[redacted]

Full details of the safety analyses will be specified in the formal Statistical Analysis Plan.

11.8 Interim Analysis

No interim analysis is planned for this study.

11.9 Missing Data

There will be no imputations for missing data.

11.10 Adjustment for Multiplicity

There will be no adjustments for multiplicity.

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 froman 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 [redacted] 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 [redacted] and/or the sponsor and provided in writing by [redacted] 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 [redacted] 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 the 6-digit kit number listed on the kit. The primary packaging of the LNZ101, LNZ100, and Vehicle Ophthalmic Solution will be blow-fill-seal ampoules.

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, at temperature 2-8ºC. 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

For in-office dosing, the IP is to be administered by study site personnel, and is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP administered to subjects and the amount returned or disposed throughout the course of the study. A detailed inventory must be completed for the IP.

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 at Visit 7 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 inthe study. Authorship will be established before writing the manuscript. [redacted] and the study sponsor will have the final decision regarding the manuscript and publication.

13.0 REFERENCES

Francois J. and Goes F. Ultrasonic study of the effect of different miotics on the eye components. Ophthalmologica Basel 1977;175(6):328-338.

Gilmartin, B., A. C. Amer and S. Ingleby (1995). "Reversal of tropicamide mydriasis with single instillations of pilocarpine can induce substantial pseudo-myopia in young adults." Ophthalmic Physiol Opt 15(5): 475-479.

Helmholtz, H.v. Uber die akkommadation des auges. A. v. Graefe's Arch. Klin. Ophthlmol. 1855;1, 1 74.

Holden B, Fricke T, Ho S, Wong R, Schlenther G, Cronje´ S, Burnett A, Papas E, Naidoo K,Frick K. Global vision impairment due to uncorrected presbyopia. Archives of Ophthalmology 2008;126(12):1731-1739.

Ostrin, L.A. and Glasser, A Edinger-Westphal and pharmacologically stimulated accommodative refractive changes and lens and ciliary process movements in rhesus monkeys. Experimental Eye Research 2007;84: 302-313.

Randazzo A, Nizzola F, Rossetti L, Orzalesi N, Vinciquerra P. Pharmacological management of night vision disturbances after refractive surgery Results of a randomized clinical trial. J Cataract Refract Surg 2005;31(9): 1764-1772.

Romano, J. H. Double-blind cross-over comparison of Aceclidine and Pilocarpine in open-angle glaucoma. British Journal of Ophthalmology 1970;54: 510-521.

Scarcelli, G., Kim, P., and Yun, S.H. In vivo measurement of age-related stiffening in the crystalline lens by 51rillouin optical microscopy. Biophysical Journal 2011;101: 1539-1545.

Truscott, R. J. Presbyopia. Emerging from a blur towards an understanding of the molecular basis for this most common eye condition. Experimental Eye Research 2009;88: 241-247.

14.0 APPENDICES

Appendix 1: Schedule of Visits and Measurements

For the suggested order of assesments, please refer to Section 9.3.1

Study Parameter	Visit 1 (Day -60 to Day -4)	Visit 2 (Day 1)	Visit 3 (Day 15 ± 2 Days)	Visit 4 (Day 43 ± 7 Days)	Visit 5 (Day 85 ± 7 days)	Visit 6 (Day 127 ± 7 days)	Visit 7 (Day 180 ± 14 days)
Informed consent / HIPAA	X						
Demographic data	X						
Medical and medication history	X						
Medical and medication history update		X	X	X	X	X	X
Inclusion and exclusion criteria review	X	X					
Urine pregnancy test (for females of childbearing potential)	X	X					X
Vital signs (resting blood pressure and pulse)	X			X	X		X
Physical examination[a]	X			X	X		X
Systemic labs	X			X	X		X
Manifest refraction	X						
AE query[b]	X	X	X	X	X	X	X
Monocular BCDVA at 4 m	X	X	X	X	X	X	X
Specular Microscopy	X						X
Slit lamp biomicroscopy	X	X	X	X	X	X	X
Fluorescein Staining	X[c]						
IOP	X	X	X	X	X	X	X
Dilated indirect fundoscopy	X[c]						X
Undilated fundus exam		X					
Randomization		X					
Dispense IP/dosing diary[d]		X	X	X	X	X	
Instill IP		X					
Collect IP/dosing diary[d]			X	X	X	X	X
Study exit							X

[a]Physical examination includes general health, head, eyes, ears, nose, throat, and other comments (HEENT).
[b]Asked at the beginning of Visits 2, 3, 4, 5, 6, and 7 and at the end of Visits 1, 2, 3, 4, 5, 6, and 7.
[c]Not required if conducted within previous 60 days as part of V1 for LENZ study 22-150-0015 or 22-150-0018
[d]All randomized subjects will be provided instructions on how to instill two (2) drops bilaterally, one drop in each eye followed by 2 minutes later, another drop in each eye.

Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 4: Investigator's Signature

Protocol Title: A Multi-Center, Double-Masked Phase 3 Evaluation of the Long-term Safety of LNZ101 in Presbyopic Subjects

Protocol Number: 22-150-0017

[redacted]

Signed:_____ Date:_____ [Name]

Principal Investigator

[Affiliation]