CLARA: A Phase 1/2 Multi-center, Randomized, Double-Masked, Prospective, Parallel- Arm Study of AURN001 in Subjects with Corneal Edema Secondary to Corneal Endothelial Dysfunction (ABA-1)

Investigational Product

[AURN001]

Protocol Number: ABA-1

Version: 6.0

Version Date: 23-Sep-2024

Sponsor
Aurion Biotech, Inc

117 E. Louisa Street
#561
Seattle, WA 98102

Investigator Statement of Compliance

CLARA: A Phase 1/2 Multi-center, Randomized, Double-Masked, Prospective, Parallel-Arm Study of AURN001 in Subjects with Corneal Edema Secondary to Corneal Endothelial Dysfunction (ABA-1)

The study will be carried out in accordance with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 11, Part 50, Part 54, Part 56, and Part 312) and other regional regulatory agency requirements. In addition, compliance with the International Council for Harmonization E6 Good Clinical Practice Guideline is expected. Adherence to the clauses of the Clinical Trial Agreement and proper oversight of all staff members completing any activities for the study are required.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is screened. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Accepted by:

Principal Investigator Signature	Date	Printed Name

PROTOCOL REVISION HISTORY

Date	Version	Description of Modifications	Rationale for Modification
02 March 2023	1.0	Original Issue	N/A
26 June 2023	2.0	1. Updated the number of days since cataract surgery + PC-IOL (56 to 42 days). 2. Updated the number of days since yttrium-aluminum garnet (YAG) prior to the screening visit (28 to 14 days). 3. Updated the safety information for SAE and pregnancy reporting from ICON to CTDS. 4. Updated figure number 2 to figure number 3. 5. Updated the spelling of deferoxamine throughout. 6. Updated the spelling of Goldman (sic) Tonometry to Goldmann. 7. Updated negative serum pregnancy test to urine pregnancy test. 8. Removed adverse events under Screening in the Schedule of Assessments. 9. Removed PK = pharmacokinetic from the footnotes in the Schedule of Assessments. 10. Updated language for [redacted] 11. Updated Rescue Criteria and Rescue Treatment to Standard of Care. 12. [redacted] 13. Section 4.4.1 Potential risks has been updated.	1. Corrected typo in entry criterion. 2. Corrected typo in entry criterion. 3. Based on updated reporting information for serious adverse events and pregnancy for this study. 4. Corrected typo. 5. Corrected typo. 6. Corrected typo. 7. Corrected typo in entry criterion. 8. Updated to align with the language in the body of the protocol. 9. Updated based on current protocol. 10. To clarify the [redacted] testing method. 11. Updated to meet requirements in different geographies. 12. Updated according to available equipment at sites. 13. Updated to meet requirements in different geographies.

Date	Version	Description of Modifications	Rationale for Modification
08 September 2023	3.0	1. Y-27632 pharmacokinetics assessment added. 2. 1 meter distance added for visual acuity examinations; specified through phoropter for BCVA, [redacted] 3. Adverse Events deleted from Visit 1 in Section 8.4. 4. Added sponsor observation language. 5. The treatment sequence will be randomized. 6. Updated Appendix 8.	1. To assess Y-27632 blood level changes. 2. To allow for testing at 1M where clinically indicated and to specify how [redacted] will be performed for this study. 3. Typo corrected. 4. Per IRB request. 5. To optimize the use of fresh product. 6. Reading Center Manual will provide detailed instructions for zones and locations to be captured.
19 December 2023	4.0	1. Y-27632 pharmacokinetics assessment removed. 2. Ophthalmic assessments order updated. 3. Uncorrected Visual Acuity (UCVA) examination added to multiple timepoints. 4. [redacted] Testing changed from 2.5 % to 25% Contrast Chart. 5. Added an optional 2-month visit. 6. [redacted]	1. To minimize assessments performed during the face down time. 2. To allow investigators to examine eyes according to their standard of care. 3. Updated to assess at additional timepoints. 4. Updated to align with the condition of the eyes. 5. To allow investigators to conduct an additional visit according to their standard of care follow-up. 6. To clarify requirements.
04 June 2024	5.0	1. Rescue criteria language updated to remove timeframe references.	1. To clarify that rescue can occur when clinically indicated.
23 September 2024	6.0	1. Added assessment using the [redacted] at one study site.	1. To evaluate the images collected using the newer contact version of the [redacted] at one study site.

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[redacted]

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	Adverse Event/Experience
AURN001	*Neltependocel* and Y-27632
[redacted]	[redacted]
BCVA	Best Corrected Visual Acuity
C	Celsius
CD	Compact Disc
CEC	Corneal Endothelial Cells
CFB	Change from Baseline
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
[redacted]	[redacted]
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council on Harmonization
ICF	Informed Consent Form
ID	Subject Identification
IEC	Independent Ethics Committee
IOL	Intraocular Lens
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intra-Uterine Device
[redacted]	[redacted]
LogMAR	Logarithm of the Minimum Angle of Resolution
MR	Manifest Refraction
NDA	New Drug Application
NEI	National Eye Institute
neltependocel	Allogeneic human corneal endothelial cells
NSAID	Nonsteroidal Anti-Inflammatory Drug
OCT	Optical Coherence Tomography
OD	Oculus Dexter or Right Eye

Term	**Definition**
OS	Oculus Sinister or Left Eye
PC-IOL	Posterior Chamber Intraocular Lens
PKP	Penetrating Keratoplasty
PPS	Per Protocol Set
PRO	Patient Reported Outcomes
QD	quaque die (one a day)
RAPD	Relative Afferent Pupillary Defect
SD-OCT	Spectral Domain Optical Coherence Tomography
SAE	Serious Adverse Event/Experience
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
UCVA	Uncorrected Visual Acuity
UPT	Urine Pregnancy Test
US	United States
VA	Visual Acuity
[redacted]	[redacted]
WOCBP	Women of Childbearing Potential
Y-27632	A Rho-kinase inhibitor small molecule drug
YAG	Yttrium Aluminum Garnet

2 SYNOPSIS

Protocol Title	CLARA: A Phase 1/2 Multi-center, Randomized, Double-Masked, Prospective, Parallel- Arm Study of AURN001 in Subjects with Corneal Edema Secondary to Corneal Endothelial Dysfunction (ABA-1)
Protocol Number	ABA-1
Phase of Clinical Study	1/2
Number of Investigational Sites	Approximately 10-20 sites in North America
Number of Subjects Planned	Approximately 100
Study Population	Adult subjects with corneal edema secondary to corneal endothelial dysfunction
Investigational Product (IP)	AURN001
Study Objectives	The primary objective is to evaluate: • Efficacy of a single injection of different concentrations of *neltependocel* in combination with Y-27632 (i.e., AURN001), *neltependocel* alone, and Y-27632 alone in subjects with corneal edema secondary to corneal endothelial dysfunction The secondary objective is to evaluate: • Safety and tolerability of a single injection of different concentrations of *neltependocel* in combination with Y-27632 (i.e., AURN001), *neltependocel* alone, and Y-27632 alone in subjects with corneal edema secondary to corneal endothelial dysfunction
Efficacy Endpoints	**Primary Efficacy Endpoint** • Response, defined as a ≥ 15-letter improvement (3-line gain) from baseline in best-corrected visual acuity (BCVA) at Month 6 **Secondary Efficacy Endpoints** • Change from baseline in BCVA at Month 6 • Change from baseline in central corneal thickness (CCT) at Month 6 • Response, defined as a ≥ 15-letter improvement (3-line gain) from baseline in BCVA at all other timepoints • Change from baseline in BCVA at all other timepoints • Change from baseline in CCT at all other timepoints • Response, defined as a ≥ 10-letter improvement (2-line gain) from baseline in BCVA at each timepoint **Exploratory Efficacy Endpoints** [redacted]

<table>
<tr><td>Safety Evaluations</td><td>

Incidence and severity of ocular treatment-emergent adverse events (TEAEs)
Incidence and severity of non-ocular TEAEs
Loss from baseline in BCVA ≥ 15 letters
Rescue rate
Graft rejection

</td></tr>
<tr><td>Study Design and Overview</td><td>
This is a multicenter, randomized, double-masked, parallel-arm, dose-ranging, Phase 1/2 study of AURN001 in subjects with corneal edema secondary to corneal endothelial dysfunction.

The efficacy and safety of AURN001 will be assessed in a clinical trial setting in adult subjects with corneal edema secondary to corneal endothelial dysfunction.

Three doses of AURN001 compared with the 2 components of AURN001 separately (neltependocel and Y-27632) will be evaluated to assess the contribution of these 2 elements to the efficacy and safety of AURN001.

This trial will enroll approximately 100 subjects in the 5 treatment arms with approximately 20 subjects per arm. A randomized treatment sequence will be assigned. The sponsor will assess the actual enrollment in each arm on an on-going basis throughout the study to maintain a randomization ratio of 1:1:1:1:1. The sponsor will make adjustments to the randomized treatment sequence and the number of subjects to be treated in each cohort as needed.

The treatment arms are as follows:

<table>
<tr><th>Arm</th><th>No. of Subjects</th><th>Neltependocel Dose</th><th>Y-27632 Dose</th><th>Endothelial Polishing?</th></tr>
<tr><td>1</td><td>20</td><td>1.0×10^6</td><td>100 µM</td><td>Yes</td></tr>
<tr><td>2</td><td>20</td><td>5.0×10^5</td><td>100 µM</td><td>Yes</td></tr>
<tr><td>3</td><td>20</td><td>2.5×10^5</td><td>100 µM</td><td>Yes</td></tr>
<tr><td>4</td><td>20</td><td>None</td><td>100 µM</td><td>Yes</td></tr>
<tr><td>5</td><td>20</td><td>1.0×10^6</td><td>None</td><td>Yes</td></tr>
</table>

This study will have a screening period, a surgery/treatment day during which treatment will be administered, and a 12-month observation period. The primary efficacy analysis will be conducted at Month 6.

The study will have up to 10 visits with one optional visit: the Screening Visit (Visit 1, -77 days to -7 days); Surgery/Treatment (Visit 2, Day 1); and Follow-up (Visits 3 through 10, Day 2, Week 1, Week 4, and Months 2 (optional), 3, 4.5, 6, 9, and 12, respectively). Unscheduled visits will be allowed, as deemed necessary by the investigator.
</td></tr>
</table>

	If the investigator considers it clinically appropriate, after discussion with the medical monitor, subjects who do not meet all study criteria at the Screening Visit may be rescreened within 6 weeks of the Screening Visit. In this case, baseline will be defined by the most recent measure prior to treatment. At the Screening Visit (-77 days to -7 days), subjects who sign the informed consent form (ICF) will undergo screening procedures to determine their eligibility to participate in the study. Surgery will be scheduled in accordance with the manufacturing and delivery schedule of fresh investigational product. The investigators, subjects, and all study site personnel will remain masked to study treatment throughout this process. Only one eye of each subject will receive treatment based on the ocular eligibility criteria; the treated eye will be designated as the "study eye." If both eyes qualify for treatment, the study eye will be selected at the investigator's discretion, in consultation with the Medical Monitor, based on the eye where visual acuity is most affected by corneal edema. The other eye will be designated as the "non-study eye. Although only one eye is being treated, it is important to note that both eyes will undergo all ocular assessments as outlined in the Schedule of Assessments.
IP Mode of Administration	Subjects assigned to active treatment will receive a single injection of AURN001 (*neltependocel* with Y-27632), *neltependocel* alone, or Y-27632 alone into the anterior chamber of the study eye. The dose of *neltependocel* will be either 1.0×10^6, 5.0×10^5 or 2.5×10^5; the dose of Y-27632 will be 100 µM. The total volume of administration will be approximately 300 µL. **Surgical Procedure**: The injection of study treatment into the study eye will be performed under local anesthesia (administration method at the investigator's discretion). After creating a small incision at the corneal limbus, the corneal endothelium will be polished to a diameter of approximately 8 mm. Study treatment will be injected into the anterior chamber using a 27-gauge needle. Immediately after completion of surgery, subjects will lie face down for approximately 3 hours (±15 minutes). For detailed instructions, please refer to the Procedure Manual, which includes Sponsor observation language.
Inclusion Criteria	Subjects must meet all of the following criteria to be eligible for study participation: ***General Criteria*:** 1. Be 18 years of age or older at the time of signing consent. 2. Able to understand and willing to sign an ICF approved by an Institutional Review Board. 3. Are willing and able to lie face down for approximately 3 hours (±15 min) immediately after the surgical procedure on Day 1. 4. Are reliable and willing to comply with study instructions and return for all scheduled examinations post-operatively.

	5. Women of child-bearing potential must have a negative urine pregnancy test at the Screening Visit and be willing to use birth control, as described below: All subjects of child-bearing potential, male and female, must agree to use a reliable method of birth control for the entire duration of the study (i.e., 12 months post treatment). Acceptable methods of birth control include oral contraceptives; implantable contraceptives; injectable contraceptives; a contraceptive patch; barrier methods such as diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, or intrauterine devices; a partner with vasectomy. Birth control is not required if the female is infertile due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy, hysterectomy, or at least 6 weeks after tubal ligation) confirmed by medical history or menopause (after at least 12 consecutive months from last menstruation). Post-menopausal females are not required to use birth control. Men are eligible to participate if they agree to the following for the entire duration of the study (i.e., 12 months post treatment): a. Refrain from donating sperm. b. For men with partners of childbearing potential or partners who are pregnant or breastfeeding: Use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant. ***Ocular Criteria in the Study Eye:*** 6. Have a diagnosis of corneal edema secondary to corneal endothelial dysfunction, requiring surgery (full- or partial-thickness endothelial keratoplasty). 7. Be pseudophakic with a posterior chamber intraocular lens (PC-IOL) located fully within the capsular bag without evidence of zonular instability. 8. Have at least 42 days (6 weeks) since cataract surgery + PC-IOL, a minimum of 14 days (2 weeks) since yttrium-aluminum garnet (YAG) capsulotomy prior to screening visit. 9. BCVA between 65 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (i.e., 0.4 LogMAR or approximate 20/50 Snellen equivalent) and 5 ETDRS letters (i.e., 1.6 LogMAR or approximate 20/800 Snellen equivalent). 10. Have a CCT in the study eye of less than 1000 microns and greater than 575 microns. If CCT is less than 575 microns, must have other documented clinical findings of corneal edema (i.e., Descemet's folds, bullous keratopathy, microcystic edema, or stromal haze).

Exclusion Criteria	Subjects will not be eligible for study participation if they meet any of the following criteria at screening: ***General Criteria*** 1. History of human immunodeficiency virus or hepatitis B. 2. Have current systemic infection or inflammation that may require antiviral therapy that will not be completed prior to the Screening Visit, or that in the opinion of the investigator and with concurrence of the Medical Monitor, may either put the subject at risk or may influence the results of the study, or the subject's ability to participate in the study. 3. History of malignancy within 1 year, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. 4. Women who are pregnant or breastfeeding. 5. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted. 6. Have a history of any clinically significant disease or disorder, ocular or otherwise (e.g., uncontrolled systemic disease such as diabetes mellitus) which, in the opinion of the investigator, may put the subject at risk for study participation, influence the results of the study, or affect the subject's ability to participate in the study. ***Ocular Criteria*** 7. Have conditions associated with clinically meaningful corneal thinning/ectasia in the study eye (for example, keratoconus). 8. Have progressive stromal or anterior corneal dystrophies or degenerations in the study eye. 9. Have pre-operative corneal epithelial, sub-epithelial or stromal scarring or other opacity that is paracentral/central and visually significant, but not suspected to be secondary to corneal endothelial disease with the potential to improve from treatment in the study eye. 10. Have visually significant posterior capsule opacification in the study eye. YAG posterior capsulotomy should be performed prior to screening where clinically indicated. 11. Have prior history of corneal transplantation, glaucoma (e.g., trabeculectomy, valve), or vitreoretinal surgery, aphakic, anterior chamber-IOL, or iris claw IOL, in the study eye. 12. Have evidence of vitreous prolapse into the anterior segment of the study eye or zonular instability in the study eye. 13. Have uncontrolled glaucoma or intraocular pressure greater than 24 mmHg that is not controlled with medication or surgery at the time of the Screening Visit. 14. Have uncontrolled co-morbidities of the ocular surface, and/or anterior segment, such as ocular surface disease, exposure keratopathy, visually significant or symptomatic pterygium, or clinically significant vascularized cornea in the study eye.

	15. History of or findings consistent with active or prior uveitis in the study eye. 16. Have a history of or current evidence of ocular herpetic diseases (including herpes simplex virus, varicella zoster or cytomegalovirus) in the study eye. 17. Have history or presence of an ocular disease other than corneal endothelial dysfunction that could affect vision or safety assessments. 18. Have relative afferent pupillary defect (RAPD). 19. Monocular ***Medications*** 20. Have used medications known to be toxic to the cornea, retina, lens, or optic nerve within 1 month prior to the Screening Visit. These medications include, but are not limited to, carbonic anhydrase inhibitors [systemic or topical ophthalmic]; amiodarone; indomethacin; chloroquine/hydrochloroquine; isotretinoin [Accutane™]; belantamab mafodotin or other antibody-drug conjugates used for immunotherapy; deferoxamine; chlorpromazine; phenothiazines; tamoxifen; and ethambutol. 21. Have known hypersensitivity or allergy to fluorescein (e.g., bronchospasm, rash, etc.) or to any component of the study products or a contraindication to dilation of the pupil; mild allergies without angioedema or need for treatment may be acceptable if deemed not to be of clinical significance in the opinion of the investigator (including but not limited to mild seasonal hay fever).
Rescue Therapy	**RESCUE CRITERIA:** Subjects whose clinical status declines in the study eye may be evaluated for rescue surgery by Standard of Care Keratoplasty [Descemet membrane endothelial keratoplasty (DMEK), Descemet stripping endothelial keratoplasty (DSEK), or penetrating keratoplasty (PK)]. Consultation with the Medical Monitor is required prior to any procedure. Evaluation will include the subject's visual symptoms, problems, or complaints, and ocular examination findings as available. Subjects who undergo a rescue procedure should be followed for approximately 1 month and may be discontinued from the study thereafter. All decisions involving rescue surgery should be documented in the eCRF. In addition, all post-rescue follow-up visits should be documented in the eCRF.
Efficacy and Safety Assessments	The efficacy evaluation will be based on measurements of BCVA (using ETDRS), ultrasonic contact pachymetry, [redacted], The safety evaluation will be based on adverse event (AE) reporting, laboratory findings (clinical chemistry and hematology), and ophthalmic examinations, including Goldmann tonometry, Slit Lamp biomicroscopy, gonioscopy, dilated fundoscopy, and BCVA (as measured by ETDRS). All ocular assessments will be conducted on both eyes.

Sample Size Considerations	This sample size is based on clinical feasibility and adequate size to characterize safety in the study population, without consideration for statistical power.
Statistical Methods	**Analysis Sets** The Full Analysis Set (FAS) will be defined as all eligible subjects who received any amount of study drug during intracameral injection. All subjects in FAS will be analyzed according to the treatment they actually received. Per Protocol Set (PPS) is a subset of FAS who completed the study without major protocol deviations. The Safety Analysis Set will be the same as FAS. **Efficacy Analyses** For the primary endpoint and other binary endpoints, number and percentage of subjects, with associated 2-sided exact (Clopper-Pearson) 95% confidence intervals (CIs), will be presented by treatment in each category (response, non-response). The distribution of responders will be compared between treatment arms using a two-sided Fisher's exact test. Analyses of change from baseline in BCVA, CCT and [redacted] will be conducted using the Full Analysis Set and a restricted maximum likelihood based mixed-effect model for repeated measures to evaluate the effect over time. The dependent variable will be the change from baseline. The model will include treatment arm (3 levels), categorical time, treatment arm by time interaction, and baseline value as a covariate. **Safety Analyses** All safety analyses will be conducted on the Safety Analysis Set. No formal statistical tests of treatment difference are planned. AEs will be coded using the Medical Dictionary for Regulatory Activities TEAEs (i.e., AEs that begin or worsen in severity after initiation of study drug) will be summarized by treatment arm and overall in the study eye. Non-ocular TEAEs will also be summarized. Additionally, TEAEs and serious AEs will be summarized in a similar manner by maximum severity and relationship to study drug and the surgical procedure. Changes from baseline of quantitative measurements (ophthalmic evaluations, laboratory findings) will be summarized by treatment arm and timepoint.

3 PRINCIPAL CONTACTS

Please refer to the Contact List provided under separate cover.

4 BACKGROUND INFORMATION

4.1 Corneal Edema Secondary to Corneal Endothelial Dysfunction

Corneal edema secondary to corneal endothelial dysfunction and ultimately cell failure is the global leading indication for keratoplasty[1]. Corneal endothelial dysfunction is a serious, debilitating condition with significant, progressive impact on patients' lives as corneal clarity gradually diminishes, and vision is lost. The main etiologies that lead to corneal endothelial dysfunction are as follows:

- Primary endothelial dystrophy (i.e., Fuchs dystrophy, posterior polymorphous corneal dystrophy, congenital hereditary endothelial dystrophy, etc.)
- Postsurgical endothelial dysfunction (i.e., pseudophakic/aphakic corneal edema, bullous keratopathy, glaucoma tube shunts, etc.)
- Graft failure or rejection (penetrating or endothelial keratoplasty [PKP or EK])
- Other causes of endothelial dysfunction (i.e., primary/secondary keratoplasty failure, endotheliitis, toxic anterior segment syndrome, etc.)

There is a wide spectrum of severity associated with all of the etiologies that lead to corneal endothelial dysfunction, and current available therapies leave significant room for improvement. While some topical therapies like hypertonic solutions are available to treat mild stages of corneal endothelial dysfunction, they are primarily treating the symptoms rather than the root cause of the disease, and therefore, may be limited in their long-term success. Alternatively, for moderate and severe stages of corneal endothelial dysfunction, EK or PKP remain the only treatment options. Issues of concern with these approaches include limited transplant material, surgical complexity, burdensome post-operative recovery, induced astigmatism, interface issues, potential need for multiple procedures, and long visual recoveries taking months.

A potential therapeutic approach which can span the disease spectrum while decreasing the risks associated with corneal transplantation is the injection of AURN001 into the anterior chamber of the eye. This approach allows for a replacement of the diseased endothelial cells with a healthy monolayer of new corneal endothelial cells, which are able to re-establish corneal deturgescence and overall clarity.

4.2 Investigational Product Rationale

There are no FDA-approved products for the treatment of corneal edema secondary to corneal endothelial dysfunction. The only treatment option to date to restore sight is corneal transplant surgery (PKP or EK). The current standard of care in the US is corneal transplantation including full thickness corneal transplant (penetrating keratoplasty) and more commonly lamellar corneal transplantation including Descemet stripping endothelial keratoplasty (DSAEK, DSEK) and Descemet Membrane Endothelial Keratoplasty (DMEK). All require a donor cornea, one donor cornea per host.

With the current standard of care, given the complexity of the surgical procedure, the risk of post-operative surgically induced anatomical irregularities of the cornea are common, along with other complications such as post-operative graft detachment, transplant rejection, dislocation, irregular astigmatism, and infection[2–4].

Globally, corneal transplantation is considered the most common type of organ transplantation. A systematic review of available literature and published reports from international eye banks demonstrated a considerable shortage of corneal graft tissues, estimating approximately 1 cornea available for every 70 corneas needed. Low supply of donated corneas owes to cultural barriers, lack of education, logistical problems, and lack of required expertise to process the donor tissue [5–12].

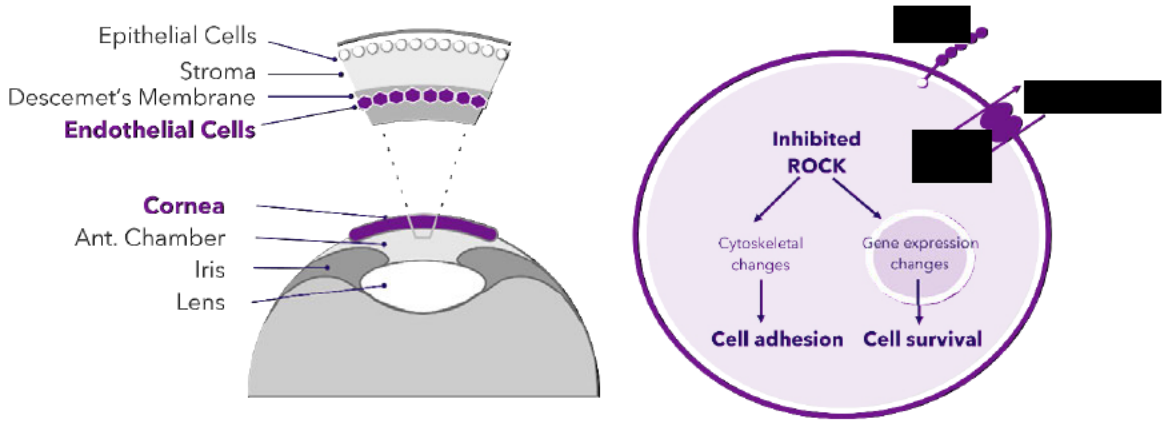
Additionally, only 47% of the world's population has access to any form of corneal transplantation. In countries where corneal transplant procedures can be accessed, median waiting time for receiving a corneal transplant was estimated about 6.5 months [interquartile range = 1 – 24 months][13].

In 2019, US eye banks supplied a total of 85,601 corneal transplants, of which 51,336 were used in the US and 28,402 used for international needs[1]. Due to the global lack of transplant tissue supply as well as limited access to surgeons who can perform a transplant, approximately 12 to 16 million people currently suffer from treatable corneal blindness without access to sight restoring transplants[7]. Due to this gap in supply and demand, more patients are added every day to the waiting lists or suffer permanent vision loss each year[14].

AURN001 is a combination product of allogeneic human corneal endothelial cells (*neltependocel*) and a small molecule drug (Y-27632, a Rho-kinase inhibitor). AURN001's corneal endothelial cells are isolated from transplantation-grade corneas and expanded ex-vivo (Figure 1). The cells harvested for AURN001 express identity marker [redacted] They also show the presence of [redacted]

The presence of Y-27632 in the formulation enhances the cells adhesion by promoting cytoskeletal changes. Furthermore, Y-27632 activates molecular pathways that promote cell survival during delivery to the recipient's cornea, increasing the likelihood of developing a new, fully functional corneal endothelial cell layer. AURN001 is expected to replace and repair the corneal endothelial architecture and restore function, which ultimately reestablishes the fluid balance needed to reinstitute corneal clarity and improve vision[16].

Figure 1 Corneal Endothelial Cell Location and Structure with Expected Y-27632 Mechanism of Action



4.3 Nonclinical Findings

The results of nonclinical and clinical studies suggest that there are no safety issues with either drug substance, *neltependocel* or Y-27632, of AURN001, and that the minor changes in formulation do not pose a safety risk. The totality of the nonclinical and clinical data with the combination product AURN001 indicate that there are no toxicological reactions (local or systemic) observed in the toxicity studies that would preclude the clinical use of this product.

Additional details about non-clinical findings can be found in the Investigator's Brochure (IB).

4.4 Risk-Benefit Analysis

There is an unmet medical need that warrants intervention for patients in need of corneal transplants.

For patients with visually significant corneal endothelial dysfunction, the only current alternative is watchful waiting in anticipation of a suitable cornea for transplant for either penetrating (PKP) or selective endothelial keratoplasty (DSAEK, DMEK). Watchful waiting may lead to a loss of vision and a burden on the health care of the patient. Disadvantages of PKP include high rates of graft rejection, poor visual quality resulting from irregular astigmatism as well as susceptibility to trauma and suture complications. Disadvantages of EK (DSAEK and DMEK) include surgical complexity, interface haze formation, increased graft detachment rates and high rates of graft failure. While the current available keratoplasty methods are effective, they are complex procedures that require a supply of donor corneas in a 1:1 ratio.

In order to address this medical need, *in vitro* expansion of human CECs is being evaluated as an alternative. This method to prepare human CECs *in vitro*, which can be transferred to the eye, is used to produce AURN001. Additional benefits of this method include smaller surgical incisions that are utilized to deliver treatment without relying on partial or full-thickness donor corneal tissue as carriers for the endothelial cell graft. Thus, in addition to being able to reach a much higher population of patients in need of corneal transplantation, human CEC injection has the

potential to reduce the risk of surgically induced complications, including corneal irregularities and the risk of post-operative graft detachment and/or dislocation of partial or full thickness corneal grafts, while allowing for the potential of one donor cornea to produce cells to treat many patients. The patient experience is improved post-operatively as positioning is limited to the first few hours following surgery, unlike keratoplasty which limits the patients' mobility for several days. In addition, there is a potential lower risk of graft rejection with AURN001 compared with EK or PKP.

In summary, the benefit-risk assessment is such that continued investigation in a clinical study setting is warranted.

4.4.1 Potential Risks

Potential risks can be categorized as those risks associated with intraocular surgical procedure and those risks associated with the IMP (AURN001).

Potential Risks Associated with Surgery

Potential risks associated with this intraocular procedure include loss of vision, ocular pain and/or discomfort, ocular hyperemia, dry eye, eyelid edema, increased tearing, subconjunctival hemorrhage, corneal or conjunctival abrasion, corneal ulcer, surgical wound leak, shallowing or collapse of the anterior chamber, Descemet's membrane tear, vitreous prolapse, damage to the iris or other structures, changes to the pupil, intraocular bleeding, infection, endophthalmitis, inflammation (uveitis), worsening of corneal edema, posterior capsular opacification (PCO), worsening of cataract, increased IOP, macular edema (including CME and DME), increase in vitreous opacities, posterior vitreous detachment, and retinal detachment, among others.

Potential Risks Associated with the IMP

Potential risks associated with the IMP (AURN001) include ocular pain and/or discomfort, ocular hyperemia, dry eye, failure to improve corneal edema, corneal ulcer, intraocular inflammation (uveitis), infection, endophthalmitis, increased IOP, graft rejection or failure, changes to the pupil, iris or other structures, posterior capsular opacification (PCO), worsening of cataract, increase in vitreous opacities, and macular edema (including CME and DME) among others. Although tumor formation has not been observed in any animal or clinical studies to date, this is a theoretical risk of receiving any cell therapy.

Previous Experience

In prior clinical trials conducted with AURN001 or an earlier formulation in Japan and El Salvador, the most common risks (>5% occurrence) with both the surgical procedure and IMP were as follows:

First In-Human Clinical Trial (Japan)

- Cystoid macular edema (19%)
- Increased IOP (16%)

Other Clinical Trials (Japan)

- Ocular pain (33%)
- Increased IOP (15%)
- Eyelid edema (7%)
- Increased tearing (7%)

Clinical Trials (El Salvador)

- Posterior capsular opacification (PCO) (29%)
- Pupillary disorder (9%)
- Increased IOP (7%)
- Iris disorder (6%)
- Descemet's membrane tear (6%)

Other less common risks (<5% occurrence) included dry eye, blepharitis, macular edema, and anterior chamber inflammation.

4.5 Dose Justification

Human Corneal Endothelial Cells – *Neltependocel*

In humans, the cornea has a diameter of about 11.5 mm and a thickness of 0.5 to 0.6 mm in the center and 0.6 to 0.8 mm at the periphery. Learnings from the current standard of care show that removing the dysfunctional corneal endothelial cells with a graft diameter of approximately 8 mm can improve patient outcomes.

Aurion calculated the number of cells that would be needed to restore [redacted] to normal levels [redacted] Given the current procedure involves polishing an area of the corneal endothelium of approximately 8 mm in diameter, to replace those corneal endothelial cells, one would need approximately [redacted] to effectively form the monolayer (assuming an equivalent area of polished cornea of approximately 50.27 mm^2). In order to account for potential attrition and displacement [redacted] of AURN001, approximately [redacted] are assumed to be the minimally efficacious dose of *neltependocel*.

Clinical experience from the 3 trials conducted in Japan and the two trials conducted in El Salvador identified 1.0×10^6 *neltependocel* as the most commonly used dose. This dose was found to have a favorable safety profile in conjunction with evidence of biological activity indicated by improvement in vision and reduction in corneal edema (as measured by BCVA and CCT). Lower doses of 5.0×10^5 and 2.0×10^5 were also found to be effective in improving vision and decreasing corneal edema; however, the number of subjects treated at these doses was low.

Three doses of *neltependocel* will be evaluated in this study: (1) 1.0 x 10^6 with 100 µM of Y-27632, (2) 5.0 x 10^5 with 100 µM of Y-27632, and (3) 2.5 x 10^5 with 100 µM of Y-27632. Doses will be delivered by single intracameral injection of a total volume of 300 µL. One of the important objectives of this first US clinical trial is to identify the minimally effective dose of *neltependocel*.

Rho-Kinase Inhibitor – Y-27632

Y-27632 is a novel, low molecular weight, ROCK inhibitor that is injected in conjunction with corneal endothelial cells. Y-27632 enhances the adherence of injected endothelial cells and promotes the development of fully functional corneal endothelial cells. Aurion has conducted human clinical trials in El Salvador where endothelial cells alone were injected intracamerally (n=20) and when compared with the co-injection of endothelial cells with Y-27632, biological activity of the endothelial cells alone was meaningfully diminished as measured by visual acuity improvement, decrease in corneal edema as measured by CCT, overall assessment of corneal clarity, and need for rescue therapy.

In addition, Aurion has performed ROCK activity measurements using an in-vitro biochemical assay and determined that in AURN001's matrix ([redacted]), a 100 µM concentration of Y-27632 inhibits about 95% of ROCK activity (data on file). Preclinical and clinical studies indicate that this level of ROCK inhibition is sufficient to ensure AURN001 efficacy. [redacted]

Furthermore, Aurion's safety pharmacology studies indicate that Y-27632 was well tolerated after intravenous administration of a single dose of up to 100 mg/kg in rabbits (Study 010179.001) as well as in a single dose intravenous and intracameral pharmacokinetic study in rabbits (Study 020179.002). In the doses employed in the rabbit pharmacokinetic study, which are up to 50X the equivalent of the clinical dose, systemic concentrations of Y-27632 fall below the lower limit of quantitation (LLOQ) of the pharmacokinetic assay (10 ng/mL) within 15 minutes after dosing.

Y-27632 has been evaluated in 130 subjects and over 150 procedures in human clinical trials in Japan and El Salvador at doses between 10 µM and 100 µM (single intracameral injection of a total volume of 300 µL). Most of the procedures were conducted using 100 µM dosing in combination with endothelial cells administered by single intracameral injection of a total volume of 300 µL. No systemic pulmonary or cardiovascular toxicity has been observed to date with intracameral administration. The most common adverse events seen are transient IOP elevations and focal iris changes (approximately 5% of subjects). These iris changes are generally considered to be mild and peak around 3 months after injection. As the technique for injecting endothelial cells has improved and refined, the incidence of severity of these iris changes has diminished.

The most recent ongoing clinical study, the Escalon study in El Salvador, is a randomized, double-masked, parallel group, dose ranging study of Y-27632 in 22 subjects which evaluated 10 µM, 20 µM and 100 µM of Y-27632 co-administered with 1.0 x 10^6 *neltependocel* injected intracamerally in a total volume of 300 µL. This study showed that subjects treated with 20 µM and 100 µM Y-27632 had better evidence of biological activity at six months as measured by

improvements in visual acuity and decreased in corneal edema compared to subjects treated with 10 µM Y-27632 and 1.0 x 10^6 cells. No differences in safety profile were noted between the three doses of Y-27632. Based on this study, Y-27632 seems to have a wide safety margin with most therapeutic benefit seen between 20 µM and 100 µM. Given these data, this US clinical trial will enroll subjects using 100 µM of Y-27632.

4.6 Trial Population

Approximately 100 subjects diagnosed with corneal edema secondary to corneal endothelial dysfunction will be screened and assigned to one of five treatment arms.

5 TRIAL OBJECTIVES

The primary objective of this trial is to evaluate the:

- Efficacy of a single injection of different concentrations of *neltependocel* in combination with Y-27632 (i.e., AURN001), *neltependocel* alone, and Y-27632 alone in subjects with corneal edema secondary to corneal endothelial dysfunction

The secondary objective of this trial is to evaluate the:

- Safety and tolerability of a single injection of different concentrations of *neltependocel* in combination with Y-27632 (i.e., AURN001), *neltependocel* alone, and Y-27632 alone in subjects with corneal edema secondary to corneal endothelial dysfunction

6 TRIAL DESIGN

6.1 Description of Trial

This is a multicenter, randomized, double-masked, parallel-arm, dose-ranging, Phase 1/2 study of AURN001 in subjects with corneal edema secondary to corneal endothelial dysfunction. The efficacy and safety of AURN001 will be assessed in a clinical trial setting in North America in adult subjects with corneal edema secondary to corneal endothelial dysfunction. Three doses of AURN001 compared with the 2 components of AURN001 separately (*neltependocel* and Y-27632) will be evaluated to assess the contribution of these 2 elements to the efficacy and safety of AURN001.

This trial will enroll approximately 100 subjects in the 5 treatment arms with approximately 20 subjects per arm. A randomized treatment sequence will be assigned. The sponsor will assess the actual enrollment in each arm on an on-going basis throughout the study to maintain a randomization ratio of 1:1:1:1:1. The sponsor will make adjustments to the randomized treatment sequence and the number of subjects to be treated in each cohort as needed.

The treatment arms are as follows:

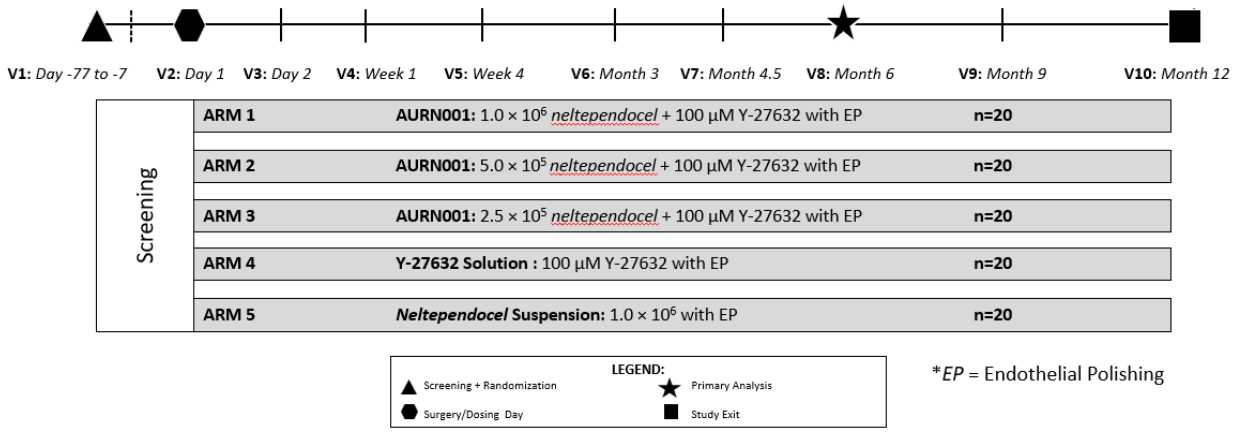
Table 1 Treatment Assignment Paradigm

Arm	No. of Subjects	*Neltependocel* Dose	Y-27632 Dose	Endothelial Polishing?
1	20	1.0×10^6	100 µM	Yes
2	20	5.0×10^5	100 µM	Yes
3	20	2.5×10^5	100 µM	Yes
4	20	None	100 µM	Yes
5	20	1.0×10^6	None	Yes

This study will have a screening period, a surgery/treatment day during which treatment will be administered, and a 12-month observation period. The primary efficacy analysis will be conducted at Month 6. The study will have up to 10 visits with one optional visit: the Screening Visit (Visit 1, -77 days to -7 days); Surgery/Treatment (Visit 2, Day 1); and Follow-up (Visits 3 through 10, Day 2, Week 1, Week 4, and Months 2 (optional), 3, 4.5, 6, 9, and 12, respectively). Unscheduled visits will be allowed, as deemed necessary by the investigator.

This study will be conducted per the schedule shown in Figure 2.

Figure 2 Study Schematic



6.2 Study Endpoints

6.2.1 Efficacy Endpoints

All ocular assessments will be conducted on both eyes. The efficacy evaluations will be based on measurements of BCVA (using ETDRS), ultrasonic contact pachymetry, [redacted]

6.2.1.1 Primary Efficacy Endpoints

- Response, defined as a ≥15-letter improvement (3-line gain) from baseline in best-corrected visual acuity (BCVA) at Month 6

6.2.1.2 Secondary Efficacy Endpoints

- Change from baseline in BCVA at Month 6
- Change from baseline in central corneal thickness (CCT) at Month 6
- Response, defined as a ≥15-letter improvement (3-line gain) from baseline in BCVA at all other timepoints
- Change from baseline in BCVA at all other timepoints
- Change from baseline in CCT at all other timepoints
- Response, defined as a ≥10-letter improvement (2-line gain) from baseline in BCVA at each timepoint

6.2.1.3 Exploratory Efficacy Endpoints

[redacted]

6.2.2 Safety Evaluations

- Incidence and severity of ocular treatment-emergent adverse events (TEAEs)
- Incidence and severity of non-ocular TEAEs
- Loss from baseline in BCVA ≥15 letters
- Rescue rate
- Graft rejection

The safety evaluations will be based on adverse event (AE) reporting, laboratory findings (clinical chemistry and hematology), and ophthalmic examinations, including Goldmann tonometry, Slit Lamp biomicroscopy, gonioscopy, dilated fundoscopy, and BCVA (as measured by ETDRS).

6.3 Randomization and Masking

This study will be double-masked and will utilize a randomized treatment sequence model. A computer-generated encrypted read-only randomized treatment sequence schedule will be provided by a biostatistician. The randomized treatment sequence schedule will be managed by unmasked team members responsible for assessing enrollment in each arm to maintain a randomization ratio of 1:1:1:1:1.

6.4 Trial Treatment

Subjects eligible to be treated will receive a single injection of AURN001 (*neltependocel* with Y-27632), *neltependocel* alone, or Y-27632 alone into the anterior chamber of the study eye. The dose of *neltependocel* will be either 1.0×10^6, 5.0×10^5 or 2.5×10^5 cells; the dose of Y-27632 will be 100 µM. The total volume of administration will be approximately 300 µL.

The injection of study treatment into the study eye will be performed under local anesthesia (administration method at the investigator's discretion). After creating a small incision at the corneal limbus, the corneal endothelium will be polished to a diameter of approximately [redacted]. Study treatment will be injected into the anterior chamber using a [redacted]. Immediately after completion of surgery, subjects will lie face down for approximately 3 hours (±15 minutes).

For detailed instructions, please refer to the Procedure Manual, which includes sponsor observation language.

6.5 Trial Duration

An individual subject's participation in the study will last approximately 12 months after injection of study drug. All subjects completing 12-month visit will be invited to participate in a long-term safety study. Data from this study will be reviewed by the Medical Monitor on an ongoing basis in a masked fashion.

6.6 Trial Material Accountability

The drug product will be supplied in [redacted]. The [redacted] is contained within [redacted] The drug product is shipped and stored at [redacted]. The drug product shipper is an insulated shipping container that is supplied and maintained by a logistics supplier. The shipper is qualified to maintain an internal temperature between [redacted].

All IP required for this study will be shipped to sites by the Contract Manufacturing Organization responsible for manufacturing the product. Product must remain in the shipper until release for injection confirmation is received and the time to administer the product is reached. The shipping container must remain upright during storage at the clinic. See Investigational Product Handling Manual for additional storage and handling instructions.

Upon receipt of the shipper, the recipient will confirm receipt. When release for injection confirmation has been received and the scheduled procedure time has been reached, the team member designated to handle and prepare the product will complete accountability of the vial.

Note: IP expires [redacted] after filling of the vial and a check of the expiry date and time must be performed prior to administering the product.

The IP must not be used outside of this study.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

This trial will include approximately 100 subjects from approximately 10-20 sites.

7.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

General Criteria:

1. Be 18 years of age or older at the time of signing consent.

2. Able to understand and willing to sign an ICF approved by an Institutional Review Board.

3. Are willing and able to lie face down for approximately 3 hours (±15 min) immediately after the surgical procedure on Day 1.

4. Are reliable and willing to comply with study instructions and return for all scheduled examinations post-operatively.

5. Women of child-bearing potential must have a negative urine pregnancy test at the Screening Visit and be willing to use birth control, as described below:

   All subjects of child-bearing potential, male and female, must agree to use a reliable method of birth control for the entire duration of the study (i.e., 12 months post treatment). Acceptable methods of birth control include oral contraceptives; implantable contraceptives; injectable contraceptives; a contraceptive patch; barrier methods such as diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, or intrauterine devices; a partner with vasectomy. Birth control is not required if the female is infertile due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy, hysterectomy, or at least 6 weeks after tubal ligation) confirmed by medical history or menopause (after at least 12 consecutive months from last menstruation). Post-menopausal females are not required to use birth control.

Men are eligible to participate if they agree to the following for the entire duration of the study (i.e., 12 months post treatment):

a. Refrain from donating sperm.

b. For men with partners of childbearing potential or partners who are pregnant or breastfeeding: Use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

Ocular Criteria in the Study Eye:

6. Have a diagnosis of corneal edema secondary to corneal endothelial dysfunction, requiring surgery (full- or partial-thickness endothelial keratoplasty).

7. Be pseudophakic with a posterior chamber intraocular lens (PC-IOL) located fully within the capsular bag without evidence of zonular instability.

8. Have at least 42 days (6 weeks) since cataract surgery + PC-IOL, a minimum of 14 days (2 weeks) since yttrium-aluminum garnet (YAG) capsulotomy prior to screening visit.

9. BCVA between 65 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (i.e., 0.4 LogMAR or approximate 20/50 Snellen equivalent) and 5 ETDRS letters (i.e., 1.6 LogMAR or approximate 20/800 Snellen equivalent).

10. Have a CCT in the study eye of less than 1000 microns and greater than 575 microns, confirmed as per standard of care. If CCT is less then 575 microns, must have other documented clinical findings of corneal edema (i.e., Descemet's folds, bullous keratopathy, microcystic edema, or stromal haze).

7.2 Exclusion Criteria

Subjects will not be eligible for study participation if they meet any of the following criteria at screening:

General Criteria

1. History of human immunodeficiency virus or hepatitis B.

2. Have current systemic infection or inflammation that may require antiviral therapy that will not be completed prior to the Screening Visit, or that in the opinion of the investigator and with concurrence of the Medical Monitor, may either put the subject at risk or may influence the results of the study, or the subject's ability to participate in the study.

3. History of malignancy within 1 year, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.

4. Women who are pregnant or breastfeeding.

5. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

6. Have a history of any clinically significant disease or disorder, ocular or otherwise (e.g., uncontrolled systemic disease such as diabetes mellitus) which, in the opinion of the investigator, may put the subject at risk for study participation, influence the results of the study, or affect the subject's ability to participate in the study.

Ocular Criteria

7. Have conditions associated with clinically meaningful corneal thinning/ectasia in the study eye (for example, keratoconus).

8. Have progressive stromal or anterior corneal dystrophies or degenerations in the study eye.

9. Have pre-operative corneal epithelial, sub-epithelial or stromal scarring or other opacity that is paracentral/central and visually significant, but not suspected to be secondary to corneal endothelial disease with the potential to improve from treatment in the study eye.

10. Have visually significant posterior capsule opacification in the study eye. YAG posterior capsulotomy should be performed prior to screening where clinically indicated.

11. Have prior history of corneal transplantation, glaucoma (e.g., trabeculectomy, valve), or vitreoretinal surgery, aphakic, anterior chamber-IOL, or iris claw IOL, in the study eye.

12. Have evidence of vitreous prolapse into the anterior segment of the study eye or zonular instability in the study eye.

13. Have uncontrolled glaucoma or intraocular pressure greater than 24 mmHg that is not controlled with medication or surgery at the time of the Screening Visit.

14. Have uncontrolled co-morbidities of the ocular surface, and/or anterior segment, such as ocular surface disease, exposure keratopathy, visually significant or symptomatic pterygium, or clinically significant vascularized cornea in the study eye.

15. History of or findings consistent with active or prior uveitis in the study eye.

16. Have a history of or current evidence of ocular herpetic diseases (including herpes simplex virus, varicella zoster or cytomegalovirus) in the study eye.

17. Have history or presence of an ocular disease other than corneal endothelial dysfunction that could affect vision or safety assessments.

18. Have relative afferent pupillary defect (RAPD).

19. Monocular

Medications

20. Have used medications known to be toxic to the cornea, retina, lens, or optic nerve within 1 month prior to the Screening Visit. These medications include, but are not limited to, carbonic anhydrase inhibitors [systemic or topical ophthalmic]; amiodarone; indomethacin; chloroquine/hydrochloroquine; isotretinoin [Accutane™]; belantamab mafodotin or other antibody-drug conjugates used for immunotherapy; deferoxamine; chlorpromazine; phenothiazines; tamoxifen; and ethambutol.

21. Have known hypersensitivity or allergy to fluorescein (e.g., bronchospasm, rash, etc.) or to any component of the study products or a contraindication to dilation of the pupil; mild allergies without angioedema or need for treatment may be acceptable if deemed not to be of clinical significance in the opinion of the investigator (including but not limited to mild seasonal hay fever).

7.3 Subject Recruitment, Screening, Rescreening and Treatment

Each subject must sign the Informed Consent Form (ICF) before his or her participation in the study. At the Screening Visit (-77 days to -7 days), subjects who sign the informed consent form (ICF) will undergo screening procedures to determine their eligibility to participate in the study. A fully signed copy of the ICF must be provided to the subject. Each subject who signs an Informed Consent Form (ICF) will be assigned a Subject Identification (ID) number consisting of a 3-digit Country Number, 3-digit Site Number, and 3-digit Subject Number (e.g., 840-001-001).

If the investigator considers it clinically appropriate, after discussion with the medical monitor, subjects who do not meet all entry criteria at the Screening Visit may be rescreened within 6 weeks of the Screening Visit. Rescreened subjects will receive a new subject ID but the previously assigned subject ID will be recorded. In this case, baseline will be defined by the most recent measure prior to treatment.

The investigators, subjects, and all study personnel will remain masked to study treatment throughout this process.

Only one eye of each subject will receive treatment based on the ocular eligibility criteria; the treated eye will be designated as the “study eye.” If both eyes qualify for treatment, the study eye will be selected at the investigator’s discretion, in consultation with the Medical Monitor, based on the eye where visual acuity is most affected by corneal edema. The other eye will be designated as the “non-study eye.”

Although only one eye will be treated, it is important to note that both eyes will undergo all ocular assessments as outlined in the Schedule of Assessments (see Appendix 1).

7.4 Withdrawal Criteria

Any subject who wishes to withdraw from participation in the study for any reason is entitled to do so without obligation. Any subject may be discontinued from study participation at the discretion of the investigator, in consultation with the Medical Monitor, or by the Sponsor for any reason.

7.4.1 Withdrawal Methods

The Sponsor may terminate this study at any time. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of adverse events (AE) in this or other studies point to a potential health hazard for trial subjects.
- Insufficient subject enrollment.
- Any information becoming available during the study that substantially changes the expected benefit risk profile of the study treatments.

7.4.2 Collection of Data from Withdrawn Subjects

In the event that study discontinuation of a treated subject is necessary, the investigator should make every attempt to have the subject complete Visit 10 (Month 12) assessments as soon as possible. The reason for premature discontinuation should be recorded in the subject chart and entered in the eCRF.

7.4.3 Subject Replacement

Subjects who withdraw will not be replaced.

8 SUBJECT TREATMENT

8.1 Treatment Regimen

Subjects will be assigned to one of five treatment arms and will receive a single injection of product. The total volume of product administered will be approximately 300 μL.

8.2 Prior and Concomitant Therapy

Table 2 List of Prohibited/Restricted Medications

Medications	Minimum Washout Period Prior to Screening (Visit 1)
carbonic anhydrase inhibitors [systemic or topical ophthalmic] amiodarone	30 days
indomethacin	30 days
chloroquine/hydrochloroquine	30 days
isotretinoin [Accutane™]	30 days

Medications	Minimum Washout Period Prior to Screening (Visit 1)
belantamab mafodotin or other antibody-drug conjugates used for immunotherapy	30 days
deferoxamine	30 days
chlorpromazine	30 days
phenothiazines	30 days
tamoxifen	30 days
ethambutol	30 days

8.3 Rescue Therapy

Subjects whose clinical status declines in the study eye may be evaluated for rescue surgery by Standard of Care Keratoplasty [Descemet membrane endothelial keratoplasty (DMEK), Descemet stripping endothelial keratoplasty (DSEK), or penetrating keratoplasty (PK)].

Consultation with the Medical Monitor is required prior to any procedure. Evaluation will include the subject's visual symptoms, problems, or complaints, and ocular examination findings as available. Subjects who undergo a rescue procedure should be followed for approximately 1 month and may be discontinued from the study thereafter.

All decisions involving rescue surgery should be documented in the eCRF. In addition, all post-rescue follow-up visits should be documented in the eCRF.

8.4 Study Assessments by Visit

Assessments should be performed as referenced in the Schedule of Assessments in Appendix 1.

Note: All ophthalmic assessments should be performed on both eyes.

8.4.1 Visit 1 (77 to 7 Days Prior to Day 1) Screening

- Informed Consent
- Demographics
- Medical/Surgical History
- Eligibility Review
- Uncorrected Visual Acuity (UCVA)
- BCVA (ETDRS) by Manifest Refraction (through phoropter) (Appendix 2)
- [redacted]

- SD-OCT (Macula)
- CCT by Ultrasonic Contact Pachymetry (Appendix 7)
- Slit Lamp Biomicroscopy
- Slit Lamp Photography
- Goldmann Tonometry (IOP) (Appendix 5)
- Gonioscopy (Appendix 6)
- Dilated Fundus Examination
- Prior/Concomitant Medications
- [redacted]
- Laboratory blood draw (hematology, chemistry) (samples to be sent to Central Lab)
- Urine Pregnancy Test (for women of childbearing potential)
- Cohort assignment

8.4.2 Visit 2 Procedure/Day 1

- Surgery/Study Treatment
- Adverse Events
- Prior Concomitant Medications

8.4.3 Visit 3 Day 2 (+2 Days)

- Uncorrected Visual Acuity (UCVA)
- Slit Lamp Biomicroscopy
- Goldmann Tonometry (IOP)
- Adverse Events
- Prior/Concomitant Medications

8.4.4 Visit 4 Week 1/Day 8 (+2 days)

- Uncorrected Visual Acuity (UCVA)
- CCT by Ultrasonic Contact Pachymetry
- Slit Lamp Biomicroscopy
- Goldmann Tonometry (IOP)
- Adverse Events
- Prior/Concomitant Medications

8.4.5 Visit 5 Week 4/Day 30 (± 7 Days)

- Uncorrected Visual Acuity (UCVA)
- BCVA (ETDRS) by Manifest Refraction (through phoropter)
- [redacted]
- CCT by Ultrasonic Contact Pachymetry
- Slit Lamp Biomicroscopy
- Slit Lamp Photography
- Goldmann Tonometry (IOP)
- Adverse Events
- Prior/Concomitant Medications

8.4.6 Visit 5.1 Month 2/Day 60 (± 7 Days) - Optional

This is an **optional visit** that can be conducted at the investigator's discretion.

- Uncorrected Visual Acuity (UCVA)
- BCVA (ETDRS) by Manifest Refraction (through phoropter)
- [redacted]
- CCT by Ultrasonic Contact Pachymetry
- Slit Lamp Biomicroscopy
- Slit Lamp Photography
- Goldmann Tonometry (IOP)
- Adverse Events
- Prior/Concomitant Medications

8.4.7 Visit 6 Month 3/Day 90 (±7 Days)

- SD-OCT (Macula)
- Uncorrected Visual Acuity (UCVA)
- BCVA (ETDRS) by Manifest Refraction (through phoropter)
- [redacted]

- CCT by Ultrasonic Contact Pachymetry
- Slit Lamp Biomicroscopy
- Slit Lamp Photography
- Goldmann Tonometry (IOP)
- Gonioscopy
- Dilated Fundus Examination
- Adverse Events
- Prior/Concomitant Medications
- [redacted]

8.4.8 Visit 7 Month 4.5/Day 135 (±14 Days)

- BCVA (ETDRS) by Manifest Refraction (through phoropter)
- [redacted]
- Slit Lamp Biomicroscopy
- Goldmann Tonometry (IOP)
- CCT by Ultrasonic Contact Pachymetry
- Adverse Events
- Prior/Concomitant Medications

8.4.9 Visit 8 Month 6/Day 180 (±14 Days)

- BCVA (ETDRS) by Manifest Refraction (through phoropter)
- Uncorrected Visual Acuity (UCVA)
- [redacted]
- SD-OCT (Macula)
- CCT by Ultrasonic Contact Pachymetry
- Slit Lamp Biomicroscopy

- Slit Lamp Photography
- Goldmann Tonometry (IOP)
- Gonioscopy
- Dilated Fundus Examination
- Adverse Events
- Prior/Concomitant Medications
- [redacted]
- Laboratory blood draw (hematology, chemistry; samples to be sent to Central Lab)

8.4.10 Visit 9 Month 9/Day 270 (±14 Days)

- BCVA (ETDRS) by Manifest Refraction (through phoropter)

[redacted]

- CCT by Ultrasonic Contact Pachymetry
- Slit Lamp Biomicroscopy
- Slit Lamp Photography
- Goldmann Tonometry (IOP)
- Adverse Events
- Prior/Concomitant Medications
- [redacted]

8.4.11 Visit 10 Month 12/Day 360 (±14 Days)

- BCVA (ETDRS) by Manifest Refraction (through phoropter)
- Uncorrected Visual Acuity (UCVA)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- SD-OCT (Macula)
- CCT by Ultrasonic Contact Pachymetry
- Slit Lamp Biomicroscopy

- Slit Lamp Photography
- Goldmann Tonometry (IOP)
- Gonioscopy
- Dilated Fundus Examination
- Adverse Events
- Prior/Concomitant Medications
- [redacted]
- Laboratory blood draw (hematology, chemistry; samples to be sent to Central Lab)

8.4.12 Unscheduled Visits

An unscheduled visit may be performed during the course of the trial in order to ensure subject safety.

All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages.

Evaluations that may be conducted at an Unscheduled Visit may include:

- BCVA assessment (through phoropter)
- Slit Lamp Biomicroscopy
- Slit Lamp Photography
- Assessment of AEs
- Assessment of concomitant medications and/or treatments
- Any other assessments needed in the judgment of the investigator

9 ADVERSE EVENTS

The investigator and study staff are responsible for detecting and recording AEs and SAEs, during scheduled safety evaluations and whenever such information is brought to their attention.

This section of the protocol provides definitions and detailed procedures to be followed.

During each visit, the investigator will question the subject about adverse events using an open question taking care not to influence the subject's answers. Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided. At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff in the ICF for reporting AEs and medical emergencies.

9.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after IP administration even though it may have been present prior to the start of the study.
- Signs, symptoms of a drug interaction

9.2 Definition of Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.

  Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
  a. Hospitalizations for elective surgeries do not constitute an SAE.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered SAEs, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above.

9.3 Disease-Related Events or Outcomes Not Qualifying as AE/SAE's

Any clinical findings associated with lack of efficacy of the IP are not considered AEs.

9.4 Monitoring and Recording of AEs and SAEs

9.4.1 Adverse Events

Any AE experienced by the subject from Visit 2 (Day 1) through Visit 10 (Month 12) is to be recorded in the eCRF, regardless of the severity of the event or its relationship to study treatment.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented.

Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started).

9.4.2 Serious Adverse Events

Any SAE experienced by the subject from Visit 2 (Day 1) through Visit 10 (Month 12) is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment.

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the investigator until the event has resolved, stabilized, or returned to baseline status.

9.4.3 All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 9.2.
- The severity of the event as defined in Section 9.7.1.
- The relationship of the event to study treatment as defined in Section 9.7.2.

9.5 Immediate Reporting of Serious Adverse Events and Pregnancies

In order to adhere to all applicable laws and regulations for reporting an SAE or pregnancy, the study site must formally notify the pharmacovigilance team within 24 hours of the study site staff becoming aware of the SAE or pregnancy. It is the investigator's responsibility to ensure that the SAE or pregnancy reporting information is emailed as described in Figure 3. It may be necessary for the pharmacovigilance team to directly communicate with the investigator if additional information is required.

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to the pharmacovigilance team on the subject's condition within 24 hours. New or updated information will be recorded on the SAE reporting form. The updated SAE reporting form should be sent to the pharmacovigilance team within 24 hours.

All additional follow-up evaluations must be reported to the pharmacovigilance team. Such data should be sent by email (Figure 3) within 10 calendar days. All SAEs will be followed until the investigator and Sponsor agree that the event is satisfactorily resolved.

Figure 3 Reporting Information for SAEs and Pregnancies

To report initial or follow up SAE or Pregnancy information email a copy of the SAE or Pregnancy report form to the following:

Safety

Email: safety@aurionbiotech.com

Phone: +1.857.639.4165

9.6 Death

The death must be recorded on the appropriate eCRF. All causes of death must be reported as SAEs. The investigator should make every effort to obtain and send death certificates and autopsy reports to the pharmacovigilance team.

9.7 Evaluating AEs and SAEs

9.7.1 Severity

The following definitions should be considered when evaluating the severity of AEs and SAEs.

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.

For AEs that change in intensity, the start and stop date of each intensity should be recorded.

An AE that is assessed as severe should not be confused with a SAE. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 9.2 Definition of a SAE.

9.7.2 Relationship to Investigational Product or Procedure

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study product or procedure:

Definitely Related	Event with plausible time relationship to product/procedure Cannot be explained by disease or other drugs Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacologic phenomenon)
Probably Related	Event with reasonable time relationship to product administration/procedure Unlikely to be attributed to disease or other drugs
Possibly Related	Event with reasonable time relationship to product administration/procedure Could also be explained by disease or other drugs
Not Related	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanation

9.7.3 Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure.

9.8 Procedures for Handling Special Situations

9.8.1 Pregnancy

Females should not become pregnant during the study period. If this occurs the subject should notify the investigator immediately. The investigator must report the pregnancy as outlined in Section 9.5. In addition, the investigator or study site staff must report the outcome of the pregnancy to the pharmacovigilance team.

9.8.2 Unmasking for Medical Emergencies

The need to unmask is not expected for this trial. If a need for unmasking arises, the treatment assignment may be unmasked and made available to the investigator, sponsor, and/or other study personnel involved in the conduct of the study, according to Unmasking Procedure (or other documents as applicable). In the absence of medical need, the treatment assignment will not be available to the above individuals until after the study is completed and the database is locked.

In the event of a medical need, the investigator will treat each subject, as medically required. If the investigator feels it is necessary to unmask a subject's treatment assignment after an emergency situation, the investigator may call the Medical Monitor and notify the Sponsor. The treatment assignment will be revealed on a subject-by-subject basis with the approval of the Medical Monitor and Sponsor, leaving the masking of the remaining subjects intact. The Sponsor

will make the final determination if the unmasking request will be granted. Once the unmasking request is granted the investigator will be provided with the treatment assignment. The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol.

9.8.3 Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the investigator or the Sponsor to be associated to the study treatment administered. The Sponsor will report SUSARs to the appropriate authorities within the required regulatory timeframes. Reports of SUSARs will be made to IRBs, and investigators, as needed.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Study Reporting

There will be two reporting events for this study, one reporting when all subjects complete Month 6 visit and another reporting when all subjects complete the study. For the first reporting, when all subjects complete the Month 6 visit, data will be cleaned and locked at the subject visit level. The study will be unmasked for the 6 months efficacy and safety analyses. For the second data reporting, when all subjects complete the entire study, data will be cleaned, and the database will be locked.

10.2 Statistical Methods

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum and maximum. Summaries for discrete variables will include frequencies and percentages. The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment.

10.3 Unit of Analysis

The unit of analysis in this study will be the study eye for all efficacy and ocular safety summaries. Additionally, non-ocular adverse events (AEs) and medical history will be presented at the subject level.

The non-study eye safety summaries will also be presented as appropriate.

10.4 Sample Size Determination

This study is not powered to show statistical significance but will provide initial estimates and trends of the endpoints for use in future trial designs. The sample size will allow for safety information to be obtained, while still limiting the number of subjects exposed to the IP. Statistical analyses will be descriptive.

10.5 Analysis Sets

The Full Analysis Set (FAS) will be defined as all eligible subjects who received any amount of study drug during intracameral injection. All subjects in FAS will be analyzed according to the treatment they actually received.

Per Protocol Set (PPS) will be defined as all subjects completing the study without major protocol deviations.

The Safety Analysis Set will be the same as FAS.

10.6 Statistical Significance

All statistical testing will be done at the two-sided alpha level of 0.05. As this is a Phase 1/2 study, no adjustments to alpha will be made for testing of multiple comparisons and multiple endpoints. Statistical analyses will be descriptive.

10.7 Efficacy Analyses

For the primary endpoint and other binary endpoints, number and percentage of subjects, with associated 2-sided exact (Clopper-Pearson) 95% confidence intervals (CIs), will be presented by treatment in each category (response, non-response). The distribution of responders will be compared between treatment arms using a two-sided Fisher's exact test.

Analyses of change from baseline in BCVA, CCT and [redacted] will be conducted using the full analysis set and a restricted maximum likelihood based mixed-effect model for repeated measures to evaluate the effect over time. The dependent variable will be the change from baseline. The model will include treatment arm, categorical time, treatment arm by time interaction, and baseline value as a covariate.

10.8 Safety Analyses

All safety analyses will be conducted on the Safety Analysis Set. No formal statistical tests of treatment difference are planned.

AEs will be coded using the Medical Dictionary for Regulatory Activities TEAEs (i.e., AEs that begin or worsen in severity after initiation of study drug) will be summarized by treatment arm and overall, in the study eye. Non-ocular TEAEs will also be summarized. Additionally, TEAEs and serious AEs will be summarized in a similar manner by maximum severity and relationship to study drug and the surgical procedure.

Changes from baseline of quantitative measurements (ophthalmic evaluations, laboratory findings) will be summarized by treatment arm and timepoint.

11 STUDY MANAGEMENT AND DATA COLLECTION

11.1 Confidentiality

All trial subject data collected and processed for the purposes of this trial 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 CRO drug safety, the Sponsor, the IRB/IEC approving this trial, 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 trial subject's original medical and trial 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 trial may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.2 Source Documents

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's trial subject files, as well as the results of diagnostic tests such as SD-OCT. The investigator's electronic copy of the eCRFs serves as the investigator's record of a subject's trial-related data.

11.3 Case Report Forms

All subject data will be captured in the subject source documents which will be transcribed to the eCRFs. The investigator is responsible for ensuring that trial data is completely and accurately recorded on each subject's eCRF, source documents, and all trial-related materials. All trial data should also be attributable, legible, contemporaneous, original, accurate and complete. Recorded data 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.

Data entry of all screened and treated subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff that have been trained on the system and have access to the system. Minimal data will be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the trial and database lock, compact discs (CDs) or similar media containing copies of all applicable subjects' eCRFs will be provided to each investigator site to be maintained on file by the investigator.

11.4 Records Retention

All trial related correspondence, subject records, consent forms, record of the distribution and use of all IP and copies of case report forms should be maintained on file for at least 2 years in the US, and 15 years in Canada, 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 2 years in the US, and 15 years in Canada, 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. The investigator must notify the Sponsor prior to destroying trial documentation even after the above-mentioned time has passed.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping trial 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 STUDY MONITORING, AUDITING, AND INSPECTING

12.1 Study Monitoring Plan

Each investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by the Sponsor, prior to seeking approval from the IRB/Ethics Committee. Investigators' proficiency in observing and scoring ophthalmic observations will be established and documented via review of academic training and experience, prior to examining subjects. Each investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. During study conduct, Sponsor and/or its representative will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors may review source documents to confirm that the data recorded on the electronic case report forms (eCRFs) are accurate. Further details of the trial monitoring (including medical monitoring) will be outlined in a monitoring plan.

The investigator and institution will allow Sponsor, monitors or its representatives and appropriate regulatory authorities direct access to source documents and CRFs to perform this verification. Data Managers will also review data and may interact with site personnel for clarifications.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

13 ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of International Council on Harmonization, Good Clinical Practice Guideline, Research Ethics Committee regulations, any applicable government regulations, Trust and Research Office policies and procedures.

This protocol, the ICF, relevant supporting information, and all types of subject recruitment or advertisement information must be submitted to the IRB/Ethics Committee for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB/Ethics Committee prior to implementing changes in the study. The investigator is responsible for keeping the IRB/Ethics Committee apprised of the progress of the study, any SAEs, and any changes made to the protocol according to the requirements of the site's IRB.

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Appendix 1 Schedule of Assessments

Study Period	Screening Visit	Observation Period										
		Day 1/ Procedure	Day 2	Week 1	Week 4	Month 2 (optional)	Month 3	Month 4.5	Month 6	Month 9	Month 12 / Study Exit	Un-scheduled Visit
Visit Number	**1**	**2**	**3**	**4**	**5**	**5.1**	**6**	**7**	**8**	**9**	**10**	
Study Day (D) or Week (W)/ Visit Window	**-77 to -7**	**D1**	**D2 (+2d)**	**D8 (+2d)**	**D30 (±7d)**	**D60 (±7d)**	**D90 (±7d)**	**D135 (±14d)**	**D180 (±14d)**	**D270 (±14d)**	**D360 (±14d)**	**N/A**
Informed Consent	X											
Demographics	X											
Medical/Surgical History	X											
Eligibility Review	X											
Cohort Assignment	X											
Surgery/Study Treatment		X										
Ophthalmic Assessments (To be Conducted in Both Eyes)												
UCVA [a]	X		X	X	X	X	X		X		X	(x)
BCVA (ETDRS) by MR (through phoropter) [a]	X				X	X	X	X	X	X	X	(x)
[redacted]												
SD-OCT (Macula)	X						X		X		X	(x)
CCT by Ultrasonic Contact Pachymetry	X			X	X	X	X	X	X	X	X	(x)
Slit Lamp Biomicroscopy	X		X	X	X	X	X	X	X	X	X	(x)
Slit Lamp Photography	X				X	X	X		X	X	X	(x)
Goldmann Tonometry (IOP)	X		X	X	X	X	X	X	X	X	X	(x)
Gonioscopy	X						X		X		X	(x)

Study Period	Screening Visit	Observation Period										
		Day 1/ Procedure	Day 2	Week 1	Week 4	Month 2 (optional)	Month 3	Month 4.5	Month 6	Month 9	Month 12 / Study Exit	Un-scheduled Visit
Visit Number	**1**	**2**	**3**	**4**	**5**	**5.1**	**6**	**7**	**8**	**9**	**10**	
Study Day (D) or Week (W)/ Visit Window	**-77 to -7**	**D1**	**D2 (+2d)**	**D8 (+2d)**	**D30 (±7d)**	**D60 (±7d)**	**D90 (±7d)**	**D135 (±14d)**	**D180 (±14d)**	**D270 (±14d)**	**D360 (±14d)**	**N/A**
Dilated Fundus Examination	X						X		X		X	(x)
Other Assessments												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
Laboratory blood draw (hematology, chemistry)	X								X		X	
Urine Pregnancy[b]	X	X----------									----------X	(x)

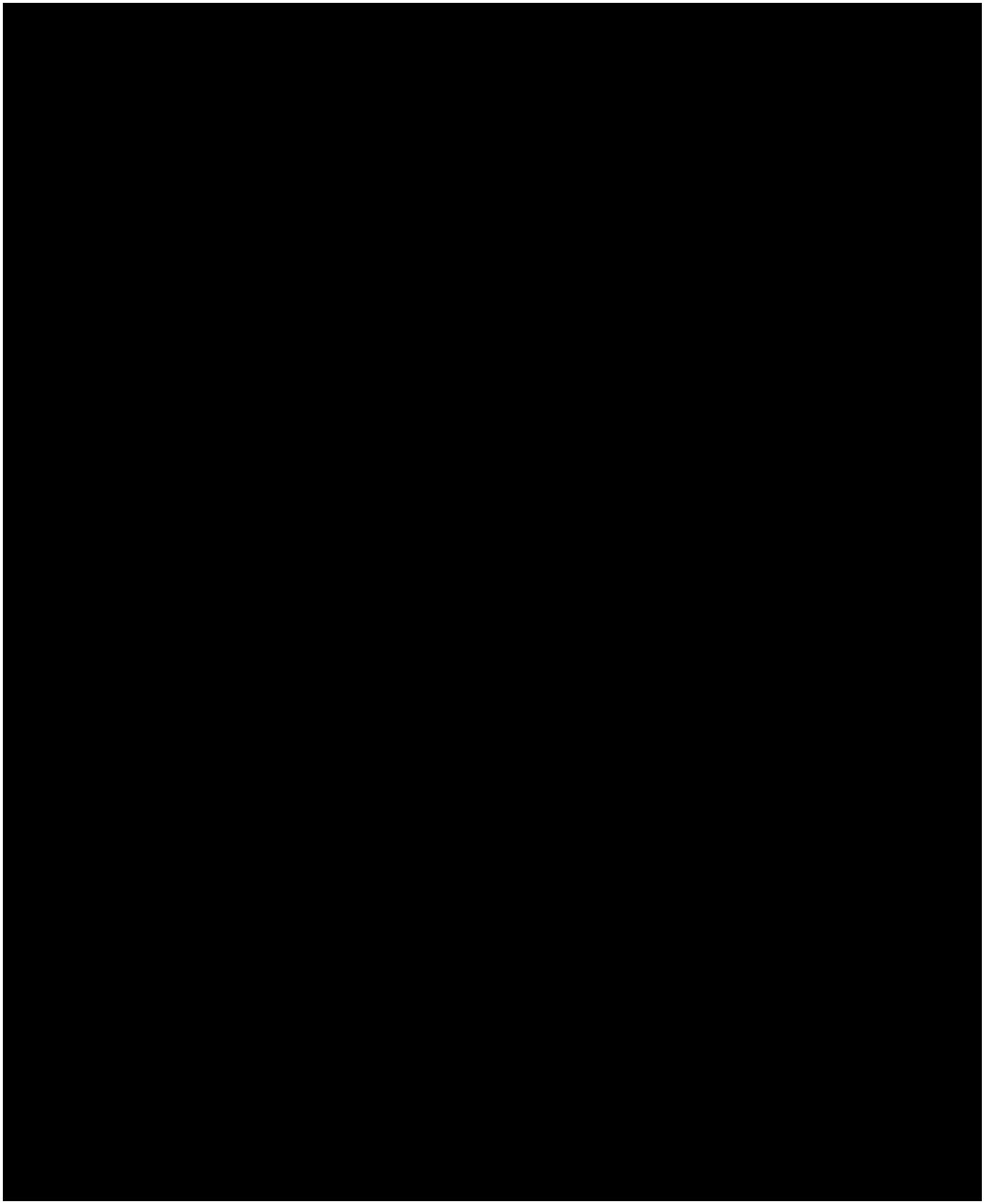
[redacted]; BCVA = best-corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; MR = manifest refraction; IOP = intraocular pressure; N/A = not applicable;; PRO = patient reported outcome; SD-OCT = spectral domain-optical coherence tomography; (x) = optional (at the discretion of the investigator); UCVA = uncorrected visual acuity; VA = visual acuity; [redacted]

[redacted]

[b.] For women of childbearing potential, a urine pregnancy test is to be conducted at the Screening Visit. Thereafter, if the subject misses 2 consecutive menstrual cycles, a urine pregnancy test is to be conducted and followed by a serum pregnancy test if the urine test is positive.

Appendix 2 Best Corrected Visual Acuity

Please refer to the Phoropter Refraction and Best-Corrected Visual Acuity (BCVA) Procedure Manual.



Appendix 5 Intraocular Pressure (IOP)

Please measure IOP with a properly sterilized Goldmann Applanation Tonometer.

1. The patient should be seated comfortably at the Slit Lamp.

2. The instrument should be calibrated by adjusting the height of the tonometer probe before initiating measurement.

3. The patient's eye is topically anesthetized.

4. The patient is asked to fixate on a target while the tonometer probe is gently placed on the cornea.

5. Operator reads the IOP value displayed on the tonometer scale. If necessary, the measurement can be repeated to obtain an average IOP value.

Note: Assessment of IOP by means other than Goldmann tonometry (e. g, air puff tonometer or tonopen) is acceptable in any event where the assessor is unable to capture an accurate measure via Goldmann applanation tonometry (i.e., poor visibility of semicircles or subject mobility issues).

Appendix 6 Gonioscopy

Slit Lamp gonioscopy is performed through a mirror. The part of the angle that is viewed is 180° away from the mirror that is being used. The examiner must remember that the image is a mirror image. The view, unlike that seen with indirect ophthalmoscopy, is not an inverted mirror image. In slit-lamp gonioscopy, the angle seen in the superior part of the temporal mirror is the superior part of the nasal angle.

One can use diffuse illumination, focal illumination with a broad beam, and focal illumination with a narrow beam. It is helpful to vary the type of illumination and the orientation of the light. Subtle findings can best be appreciated in this manner.

Please use the Schaeffer Grading System outlined in table below and note whether any clinical findings such as synechiae are present with corresponding location (i.e., number of clock hours).

Schaeffer Grading System		
Grade 4	45° to 35° angle	Wide open
Grade 3	35° to 20° angle	Wide open
Grade 2	20° angle	Narrow
Grade 1	≤10° angle	Extremely narrow
Slit	0° angle	Narrowed to slit
Grading is Based on the Angular Width of the Angle Recess		

Any observed changes from baseline should be recorded in the source document.

Appendix 7 Ultrasonic/Contact Corneal Pachymetry

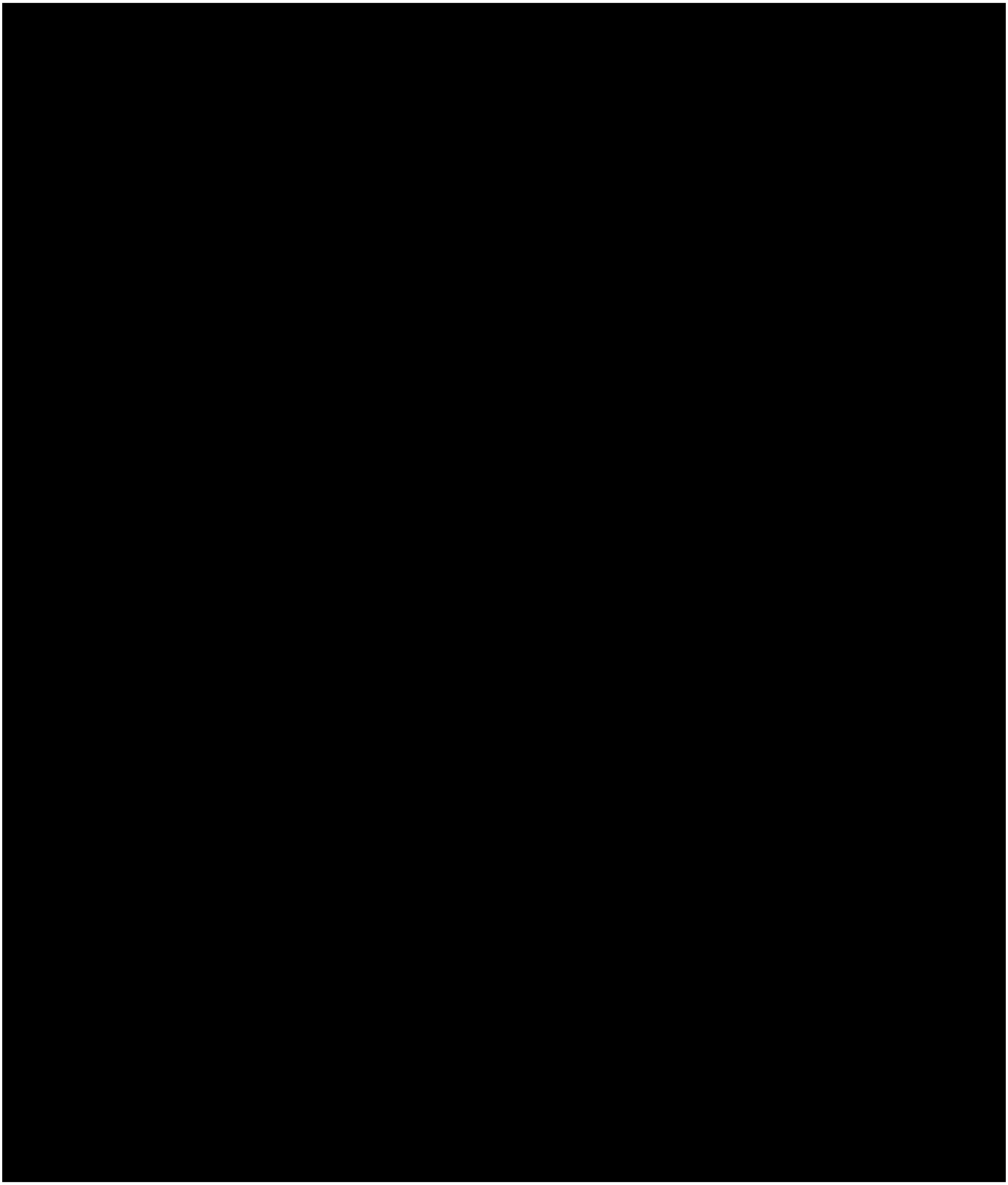
The ultrasonic pachymeter is based on traditional A-scan ultrasonography.

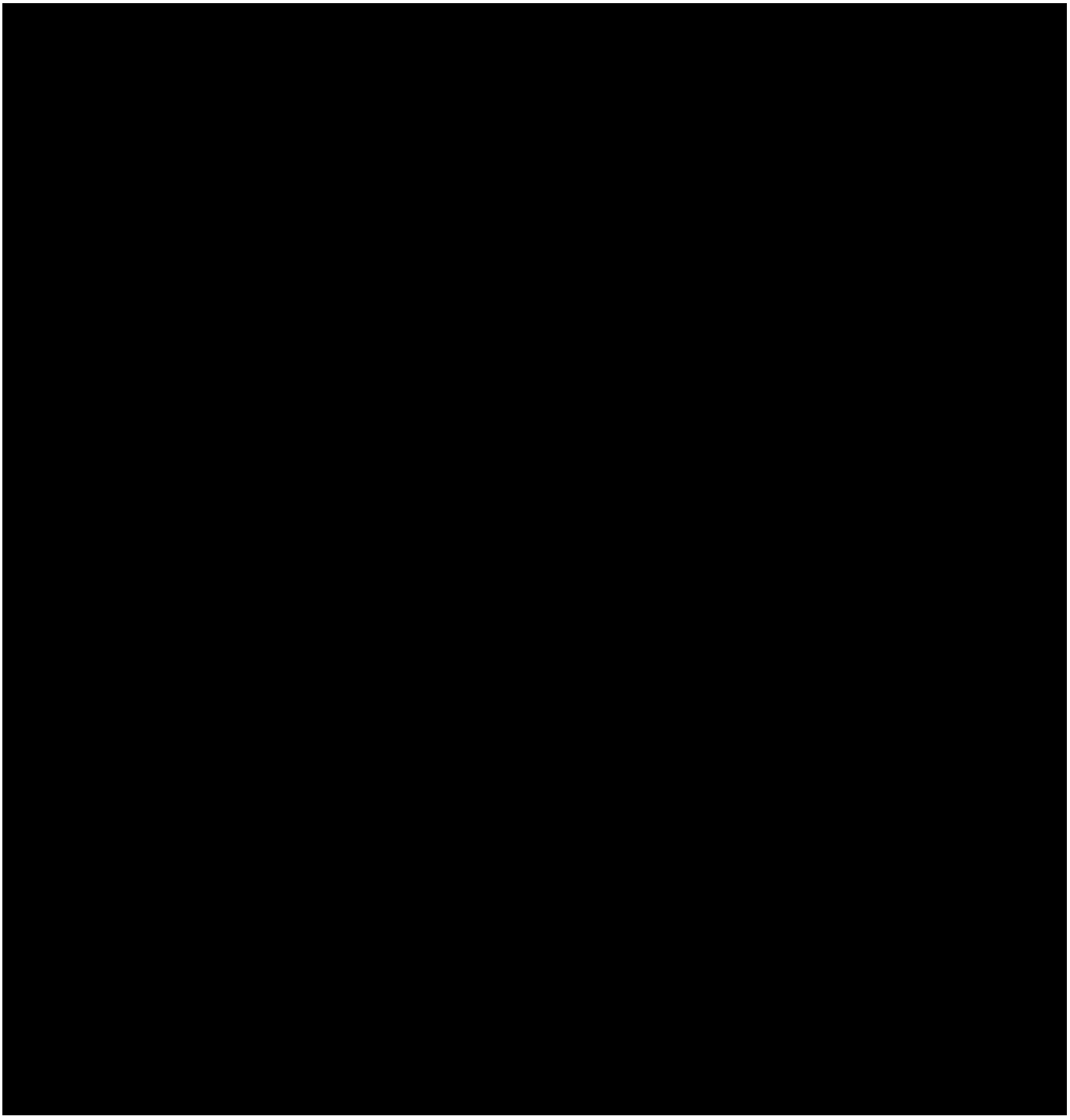
Before turning on the pachymeter, use a sterile alcohol prep pad to clean and sterilize the pachymeter probe. Let the probe tip **completely air dry** prior to use to avoid a chemical corneal abrasion from the residual alcohol. Calibrate the pachymeter, following the manufacturer instructions, before measurement.

Anesthetize both eyes. Instruct the subject to gaze straight ahead. Gently touch the **central cornea** with the probe tip, applying as little pressure as possible and **keeping the probe perpendicular** to the cornea during measurement to avoid errors. When the measurement is obtained, the probe should be withdrawn from the cornea and reapplied in the same manner for subsequent measurements.

Take a minimum of **three measurements** for each eye and record them. All three measurements should be consistent and in proximity of one another. Values are recorded in microns.

Note: If an outlier measurement is obtained, which deviates from the overall average of the other consistent values, it is important to repeat the measurement two to three times to confirm the value. Repeated measurements must be consistent in order to be considered a valid result. (Potential sources of error in measuring corneal thickness include holding the probe at an oblique angle to the cornea and measuring away from the central corneal apex, both of which would result in elevated readings of central corneal thickness (because corneal thickness increases from the center to the periphery).





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