COVER PAGE

Official Title: A Prospective Single Center Clinical Study for Femtosecond Laser Glaucoma Surgery Using the ViaLase Laser

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A Prospective Single Center Clinical Study for Femtosecond Laser Glaucoma Surgery Using the ViaLase Laser

Study Number VIA-001

Sponsor ViaLase Inc.
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This section has been redacted of personal information

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Ethics Committee Semmelweis University
39 Maria St.
Budapest, Hungary-1085
Phone: 011-36-20-815-8468

Investigator's Agreement

I have read and agree to follow the study procedures as outlined in this protocol.

_____
Print Name of Investigator

_____ _____
Investigator's Signature Date

This protocol contains confidential proprietary information with respect to the ViaLase laser and clinical trials of this product. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three (3) years from the date of this agreement, or until said information shall become a matter of public knowledge or until a formal written agreement for that purpose has been entered into by the parties.

_____ _____
Investigator's Signature Date

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A Prospective Single Center Clinical Study for Femtosecond Laser Glaucoma Surgery Using the ViaLase Laser

1. PRELIMINARY OVERVIEW

1.1 Study Synopsis

1.1.1 Administrative Information

Administrative Information	
Study Title	A Prospective Single Center Clinical Study for Femtosecond Laser Glaucoma Surgery Using the ViaLase Laser
Study Number	VIA-001
Study Sponsor	ViaLase Inc. 26800 Aliso Viejo Pkwy, Suite 225, Aliso Viejo, CA 92656

1.1.2 Study Architecture

Study Architecture	
Study Design	This is a prospective, single-center, and single arm clinical trial of ViaLase Laser for the treatment of primary open angle glaucoma. Subjects will be screened for qualification as per the inclusion/exclusion criteria and must meet the inclusion/exclusion criteria in at least one eye to be enrolled. Up to 20 subjects will be consented as per the informed consent process. Subjects will be treated with the ViaLase Laser in one eye and followed for up to 12 months. Subjects will be screened for eligibility and informed consent will be obtained from consecutive subjects who meet screening criteria and are willing to participate in the study. Eligible subjects will be examined preoperatively to obtain a medical history and to establish a baseline ocular condition. Baseline and postoperative measurements will include distance visual acuity, manifest refraction, diurnal intraocular pressure, slit-lamp examination, gonioscopy, visual field, dilated fundus examination, specular microscopy, and pachymetry. Patient will continue use of IOP-lowering medications prior to surgery and up to 1 month post-operatively. The investigator has discretion to add, continue or remove medication thereafter. This study is being conducted in accordance with good clinical practice (GCP). Protocols have been submitted to and approved by an Ethics Committee for a study in patients freely providing informed consent. Data reporting, adverse event reporting and data collection is described in this protocol.
Study Location	Semmelweis University, Budapest, Hungary

1.1.3 Study Summary

Study Summary	
Study Objective	The purpose of study is to obtain initial evidence of the safety of image guided, femtosecond laser glaucoma surgery using the ViaLase Laser for the treatment of primary open angle glaucoma.
Study Population	Subjects at least 45 years of age, of either sex, and any race or ethnicity, with refractory Primary Open Angle Glaucoma (POAG) with IOP between 21 and 35 mmHg using 1 or more IOP lowering medications.
Safety Outcomes	Immediate safety outcomes will be assessed during the Operative day (day-0), 1-day and 1-week visits: • Percentage patients with elevated IOP equal or greater than 6 mmHg at 1-hour post-treatment • Percentage of patients with iritis, anterior chamber flare and cells • Percentage of patients with Hyphema • Percentage of patients with corneal haze Additional, longer-termed, safety outcomes will be assessed by monitoring clinical data including: • Changes in best spectacle corrected visual acuity (BSCVA) • Peripheral anterior synechiae (PAS) • Cornea endothelial cell count • Endothelial cell count • Slit lamp findings • Corneal thickness (pachymetry) • Visual field • Fundus findings • Other gonioscopic findings additional to PAS • The number of glaucoma medications used • Adverse events • Procedure-related complications

<table>
<tr><th colspan="2">Study Summary</th></tr>
<tr><td>Adverse Events</td><td>All adverse events will be summarized, tabulated, and analyzed by:
Seriousness
Severity
Outcome
Relationship to the study device
Relationship to the study procedure.</td></tr>
<tr><td>Examination Schedule</td><td>The examination schedule for study subjects will be as follows:<table><tr><td>Subject Eligibility Preoperative Evaluation</td><td>1 to 60 days prior to surgery</td></tr><tr><td>Operative Evaluation</td><td>Day of surgery (Day 0)</td></tr><tr><td>Postoperative Day 1</td><td>1-day post-op</td></tr><tr><td>Postoperative Week 1</td><td>Range 5 - 9 days post-op</td></tr><tr><td>Postoperative Month 1</td><td>Range 21 - 35 days post-op</td></tr><tr><td>Postoperative Month 3</td><td>Range 70 – 105 days post-op</td></tr><tr><td>Postoperative Month 6</td><td>Range 168 – 196 days post-op</td></tr><tr><td>Postoperative Month 12</td><td>Range 330 – 420 days post-op</td></tr></table></td></tr>
<tr><td>Compliance</td><td>This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), ICH-GCP, and any regional or national regulations, as appropriate.

This may include an inspection by ViaLase representatives and/or Regulatory Authority representatives at any time. The investigator agrees to allow the inspection of study-related records by the Regulatory Authority or ViaLase representatives. Regulatory Authority approvals, authorizations, and notifications, where required, will also be in place and fully documented prior to study start.</td></tr>
</table>

1.2 Study Rationale

Glaucoma is a collection of disorders characterized by progressive loss of visual field due to optic nerve damage. It is the leading cause of global irreversible blindness effecting approximately 64.3 million people in 2013. Global estimates project the incidences of glaucoma will increase to 76.0 million in 2020 and 111.8 million people in 2040 (1). In the United States, nearly 3 million Americans have glaucoma, while another 10 million are at risk due to statistically significant elevation of the IOP (1; 2). Eyes with Primary Open-Angle Glaucoma (POAG) present elevated intra ocular pressure (IOP), though elevated IOP

is not a necessary indication for glaucomatous damage (3). It is generally bilateral, but often asymmetric. POAG is believed to be caused by an increased resistance to the normal outflow of aqueous humor from the eye. The major source of outflow obstruction that raises intraocular pressure (IOP) is thought to be the juxtacanalicular trabecular meshwork (TM), and an increase in the accumulation of extracellular material in both the TM and ciliary muscle, which further contribute to the reduction of normal outflow, resulting in increased IOP (4; 5; 6). Elevated IOP eventually leads to an acquired optic neuropathy in which the neuro retinal rim is thinned due to loss of retinal ganglion cells. When loss of optic nerve tissue is significant, patients develop optic nerve related visual field loss.

Management of glaucoma requires chronic, life-long treatment with a spectrum of therapeutic options including medications (7), laser treatment (8; 9; 10; 11), ab-interno trabeculectomy (12), and surgically implanted internal or external drainage devices (12; 13; 14; 15; 16). The common goal among the various therapies is to lower intraocular pressure (IOP) to target levels to prevent loss of visual fields from excessive pressure on the optic nerve. In order to relieve elevated IOP, it is proposed to increase the outflow through the juxtacanalicular trabecular meshwork by surgically creating canals that span from the anterior chamber, through the juxtacanalicular trabecular meshwork, and reaching the inner wall of Schlemm's canal. Such a canal can clear the outflow obstruction and provide a fluid pathway for aqueous humor.

One such therapy is the minimally invasive glaucoma surgery (MIGS) in which a trans-trabecular shunt is implanted. The interest in MIGS stems from a desire for an alternative surgical option for the treatment of glaucoma that is associated with less risk and fewer complications than established procedures. Furthermore, MIGS may help reduce the burdens of patients' compliance with medication schedules and side effects associated with medical therapy (17). Suboptimal compliance to medical therapy to manage glaucoma is common and has been linked to poor outcomes and increased health care costs.

Femtosecond lasers for ophthalmic surgery have been commercially available since 1999 (18; 19; 20). The ViaLase Laser is a femtosecond laser that is similar to other femtosecond surgical lasers, specifically, it is an infrared femtosecond laser that creates incisions in tissue using an imaging system with a live-video camera that monitors the surgical area (20; 21). The mechanism of operation and the safety profile of the ViaLase Laser is the same as other marketed femtosecond laser devices used in LASIK and cataract surgery. Unlike previous devices, the ViaLase Laser incorporates a specialized optical delivery system that directs the surgical laser and imaging light through the peripheral cornea, into the iridocorneal angle, and onto the surgical area over the trabecular meshwork (Figure 1).

The ViaLase Laser is intended to create trabecular canals or apertures to increase the flow of aqueous humor through the trabecular meshwork, juxtacanalicular tissue, and inner wall of Schlemm's canal for the treatment of open angle glaucoma.

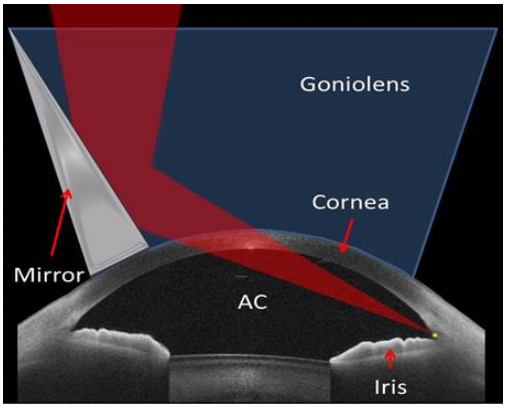

Figure 1 – Illustration showing the general optical path of the surgical beam to the iridocorneal angle.

1.3 Study Objective

To obtain initial evidence of safety of image guided, femtosecond laser glaucoma surgery using the ViaLase Laser for the treatment of primary open angle glaucoma. The ViaLase Laser is intended to create apertures through the trabecular meshwork for drainage of aqueous humor in the treatment of open angle glaucoma.

1.4 Study Design

This is a prospective, single-center, and single arm clinical trial of ViaLase Laser for the treatment of open angle glaucoma. Subjects will be screened for qualification as per the inclusion/exclusion criteria and must meet the inclusion/exclusion criteria in at least one eye to be enrolled. Up to 20 subjects will be consented as per the informed consent process. Subjects will be treated with the ViaLase Laser in one eye and followed for 12 months.

Eligible subjects will be examined preoperatively to obtain ocular and medical history and to establish a baseline ocular condition. Baseline and postoperative measurements will include distance visual acuity (best corrected), manifest refraction, intraocular pressure (IOP at baseline, 6 months and 12 months required), slit-lamp examination, gonioscopy, visual field, dilated fundus examination, specular microscopy (at baseline, 6 months and 12 months), and pachymetry.

Subjects who are on IOP lowering medications will be allowed to continue prior to laser treatment and up to one-month post-treatment. It is the investigator's discretion whether to add, continue or stop the medications after one month.

1.5 Safety Outcomes

Safety outcomes are assessed immediately after laser surgery and over 12 months after surgery.

1.5.1 Immediate Safety Outcomes

Immediate safety outcomes will be assessed during the Operative day (day-0), 1-day and 1-week visits:

- Percentage patients with elevated IOP equal or greater than 6 mmHg at 1-hour post-treatment
- Percentage of patients with iritis, anterior chamber flare and cells
- Percentage of patients with hyphema
- Percentage of patients with corneal haze

- Percentage of patients with hypotony

1.5.2 Long-Term Safety Outcomes

Additional, longer-termed, safety outcomes will be assessed by monitoring clinical data including:

- Changes in best spectacle corrected visual acuity
- Peripheral anterior synechiae (PAS)
- Cornea endothelial cell count
- Slit lamp findings
- Corneal thickness (Pachymetry)
- Visual field
- Fundus findings
- Other gonioscopic findings additional to PAS
- Adverse events
- Procedure-related complications

1.5.3 Adverse Events

All adverse events will be summarized, tabulated, and analyzed by:

- Seriousness
- Severity
- Outcome
- Relationship to the study device
- Relationship to the study procedure.

1.6 Study Population

Effectiveness endpoints for this study will be:

- The proportion of subjects with an IOP reduction of 20% or more from baseline at each post-operative visit.
- The proportion of subjects with an IOP reduction of 20% or more from baseline after 6 months while using the same number or fewer medications.

1.7 Study Population

1.7.1 Inclusion Criteria

The study eye must meet all the criteria below:

1. Diagnosis of primary open-angle glaucoma (including pigmentary and pseudoexfoliative glaucoma).
2. Glaucomatous visual field defects consistent with optic nerve defects and defined as one or more of the following:
    a. A cluster of 3 or more points in an expected location of the visual field depressed below the 5% level, at least 1 of which is depressed below the 1% level on the pattern deviation (PD) plot; or
    b. Glaucoma hemi-field test "outside normal limits"

    Note: Visual field reliability indices (i.e., fixation losses, false positives, and false negatives) should all be less than 33%. For subjects with a screening visual acuity of 20/100 or worse, a visual field is not required, and the above criteria do not need to be met.
3. Nerve abnormality characteristic of glaucoma as evaluated by clinical ophthalmoscopy defined as one or more of the following:
    a. Diffuse thinning, focal narrowing or notching of the optic disc rim especially at inferior or superior poles.
    b. Localized abnormalities of the peripapillary retinal nerve fiber layer, especially at inferior or superior poles.
    c. Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue.
4. Subject eye is phakic
    a. If **phakic**, then the crystalline lens will not have visually significant cataract that is expected to require cataract surgery within next one year. Cataract will be evaluated by using the AREDS clinical lens grading system (ARLNS). Specifically, crystalline lens must have ARLNS grade of ≤ 1.5 for signs of nuclear opalescence, cortical or posterior subcapsular opacities. Lenticular opacities not characterized by the ARLNS grading system shall also be evaluated (e.g. anterior subcapsular cataracts).
5. Mean IOP with medication at screening between 21 mmHg and 35 mmHg, inclusive.
6. Iridocorneal angle anatomy defined as follows:
    a. Trabecular meshwork visible on gonioscopy defined by Shaffer grade ≥ 3.
    b. Normal anatomy as determined by gonioscopy.
7. Light perception or better in the study eye at screening.

    Note: The non-study eye must not have a Snellen corrected visual acuity (CVA) of worse than 20/200 at screening.
8. Age 45 years or older

9. Available, willing, with sufficient cognitive awareness to comply with examination procedures and schedules.
10. Signed written informed consent.

1.7.2 Exclusion Criteria

The study eye must not meet any of the criteria below:

1. Previous glaucoma surgeries including stent implantation or other laser surgeries on study eye.
2. Prior intraocular surgery.
3. Glaucoma types as follows:
    a. Traumatic, uveitic, neovascular, or angle-closure.
    b. Glaucoma associated with vascular disorders.
4. Corneal status as follows:
    a. Any condition that would preclude safe participation in the study or reliable IOP assessments including active inflammation, edema, keratitis, keratoconjunctivitis, keratouveitis.
    b. Clinically significant dystrophy such as bullous keratopathy or Fuch's dystrophy.
    c. Guttata that would preclude safe participation in the study or reliable study assessments.
    d. Anticipated surgery of any type (including LASIK, LASEK, PRK, cataract, etc.) during the study that may alter IOP measurement.
    e. Corneal opacities or disorders that would inhibit visualization of the angle (such as severe arcus senilis).
    f. Central corneal thickness less than 440 microns or greater than 620 microns.
5. Choroid status as follows:
    a. Choroidal detachment
    b. Effusion
    c. Choroiditis
    d. Neovascularization
    e. Any active choroidopathy.
6. Retinal or optic nerve disorders, either degenerative or evolutive, that are not associated with the existing glaucoma condition including: proliferative diabetic retinopathy, central retinal artery occlusion, central retinal vein occlusion, wet age-related macular degeneration, dry age-related macular degeneration (e. g., presence of numerous large drusen associated with disturbance to or elevation of the retinal pigment epithelium), significant retinal pigment epithelial changes or optic atrophy, pathological myopia, red disease.

    Note: Minor diabetic retinopathy or hypertensive retinopathy are permitted.
7. Elevated episcleral venous pressure associated with:

a. Active thyroid orbitopathy.

b. Cavernous sinus fistula.

c. Sturge-Weber syndrome.

d. Orbital tumors.

e. Orbital congestive disease.

8. Other ocular conditions as follows:

   a. Sequelae from trauma that would preclude safe participation in the study or reliable study assessments (e.g., chemical burns, blunt trauma, etc.)

   b. Chronic ocular inflammatory disease or presence of active ocular inflammation or infection (e.g., uveitis, iritis, iridocyclitis, retinitis)

   c. Any pathology for which, in the investigator's judgement, the following would be either at risk or contraindicated:

      i. Compliance to elements of the study protocol (e.g., ophthalmic examinations, follow- up visits)

      ii. Subjects with inadequate space in the anterior chamber and/or angle as determined by slit lamp examination and gonioscopy.

9. Subject status as follows:

   a. Uncontrolled systemic disease (e.g. diabetes, hypertension) that could compromise their participation in the study.

   b. Use of systemic medications (either current, within 30 calendar days of screening exam, or anticipated) that may cause an increase in IOP, (e.g. systemic steroids including oral or IV formulation, topical steroids applied on the periorbital surface within ¼" of the external lid margins and oral inhaled steroids). Nasal inhaled steroids are allowed.

   c. Active concurrent enrollment in any investigational trial or previous participation in any investigational trial within 30 days of the screening exam.

   d. Women who are nursing, are pregnant or are of childbearing potential who refuse to use reliable contraception.

2. STUDY MATERIALS AND METHODS

2.1 Device Description

The ViaLase Laser is a precision ophthalmic surgical device designed for the creation of trabecular apertures in the treatment of open angle glaucoma. The ViaLase Laser is like other commercially available surgical femtosecond lasers in ophthalmology that use focused femtosecond laser pulses to create incisions and separate tissue. The primary difference between the ViaLase Laser and other devices is a specialized optical delivery system that focuses light into the iridocorneal angle. Like other femtosecond lasers, the ViaLase Laser creates planes of micron-sized photodisruptions sites within a volume of tissue. An incision, aperture or canal is achieved by contiguously placed micro-photodisruptions scanned by a computer-controlled delivery system.

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3. STUDY PROTOCOL

3.1 Subject Entry

Prior to enrollment in the study, the subject will be evaluated to determine eligibility. All inclusion criteria and no exclusion criterion will be met by an eligible subject. The investigator will explain the study purpose, procedures, and patient responsibilities to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined.

When it has been established that the subject may be eligible, written informed consent will be obtained. The subject will sign and date the informed consent form in the presence of a witness. The investigator or designees will also sign and date the consent form. The original will be retained with the subject records and a copy will be provided to the subject. An affidavit of Informed Consent (Appendix C) will be completed and returned to ViaLase to confirm that consent was obtained. The subject will then be considered enrolled in the study.

3.2 Informed Consent

In accordance with GCP, the Investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with prospective subjects prior to their enrollment in the study. The Investigator is responsible for obtaining written Informed Consent for each subject, prior to enrollment in the trial. A copy of the signed Informed Consent Form will be maintained in the subject's medical record or research chart, and a copy of the signed Informed Consent Form will become an integral part of each Case Report file provided to the Sponsor.

3.3 Preoperative Evaluation

Preoperative evaluation consists of two patient visits, a screening visit, and a baseline visit. During the screening visit, occurring 1 to 30 days prior to the baseline visit, the investigator informs the subject of the study and, after the subject provides consent, the investigator collects initial subject data including the subjects, demographics, ocular history, a list of ocular and non-ocular medications, and medical history. The investigator will also assess the subjects corrected visual acuity and perform a slit lamp examination.

During the baseline visit, occurring 3 to 60 days prior to the operative day, the investigator confirms the subject's list of ocular and non-ocular medications. The investigator then performs manifest refraction, best corrected spectacled visual acuity, and an endothelial cell count.

3.4 Preoperative Care

Subjects included in this study present with uncontrolled refractive Primary Open Angle Glaucoma (POAG) using 1 or more IOP lowering medications. Included subjects will be instructed to continue all current glaucoma medication.

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3.3 Postoperative Instructions

Refer to Appendix B for complete instructions associated with Methods of Clinical Evaluation.

1. Following surgery, the investigator or designee will instruct subjects to adhere to the following antibiotic/anti-inflammatory medication regimen for the study eye only:
    a. Topical antibiotic that is utilized as investigator's routine postop regiments.
    b. Continuation of glaucoma medications.
2. During the study, the discontinuation or a reduction in the dose or frequency of topical IOP lowering medication may be warranted whenever it is in the interest of patient safety. Conditions that may warrant discontinuation or frequency reduction in medication include hypotonous condition, an adverse reaction, or other systemic side effect.
3. If a pressure rise is observed, a paracentesis may be performed, as necessary. If a paracentesis is performed and there is no protocol-defined adverse event, the paracentesis will be documented in the applicable clinical report form (CRF). If, however, the paracentesis is performed and an anticipated adverse event is determined, then the AE will be recorded, and the paracentesis will be recorded on the applicable CRF as a treatment for the AE.

3.4 Examination Schedule:

Follow-up visits (as shown in Appendix A) will be scheduled over the course of 6 months. A CRF will be completed for each scheduled, unscheduled, and interim exam. Scheduled visits are defined as visits outlined in the schedule of visits. Interim visits are defined as study related visits deemed necessary by the protocol or the PI that are in addition to scheduled visits, and unscheduled visits are defined as visits that are not scheduled or interim. Subjects will be examined and evaluated according to the following scheduled visits:

3.4.1 Preoperative

- Screening - Visit 1 (range 1 – 30 days prior to Baseline)
- Baseline - Visit 2 (range 3 to 60 days prior to Operative)

3.4.2 Operative

- Surgery – Visit 3 (Day 0 occurring ≥ 3 days and ≤ 60 days after Baseline)

3.4.3 Postoperative

- Day 1 - Visit 4 (1-day post-op)
- Week 1 - Visit 5 (range 5 - 9 days post-op)
- Month 1 - Visit 6 (range 21 - 35 days post-op)

- Month 3 – Visit 7 (range 70 – 105 days post-op)
- Month 6 – Visit 8 (range 168 – 196 days post-op)
- Month 12 – Visit 9 (range 330 – 420 days post-op)

3.5 Schedule of Visits and Clinical Assessments

All required clinical assessments should be performed at each scheduled visit as specified in Appendix A. Methods for performing assessments are described in Appendix B.

For interim visits, clinical assessments that are required by the protocol or as deemed necessary by the Investigator will be conducted. Assessments will be performed according to methods described in Appendix B and recorded on an interim visit CRF. Unscheduled visit clinical assessments will be conducted according to standard of care and documented on an unscheduled visit CRF.

3.6 Subject Accounting Procedure

All consented subjects will be accounted for as follows:

1. Subject completion - Subjects are considered to have completed the study if they have completed follow-up examinations through and including 6months.
2. Screen Failure - Subjects are not considered enrolled in the study until they undergo surgery. Subjects are considered screen failures if they fail to meet screening criteria or baseline criteria as outlined in Section 1.7, or if they withdraw consent.
3. Early exit of enrolled subjects - Subjects may be exited from the investigation in the event of a condition that may cause them harm if participation were to be continued. Subjects may also withdraw voluntarily.
4. Subject lost to follow up - Subjects who do not return for their postoperative study visits and cannot be contacted within a reasonable timeframe via letter or telephone, will be considered lost to follow-up. The site will make at least three (3) telephone calls to the subject. If the three telephone contacts are unsuccessful, the site will send a registered letter with return receipt to the subject. The letter will request the subject to contact and return to the study site. If the subject is unresponsive to the first letter, the site will send a second registered letter with return receipt to the subject notifying them that they have been exited from the study due to lack of response on the part of the subject to the telephone calls and first registered letter. The site will then exit the subject from the study and the subject considered lost to follow- up. All attempts at contacting the subject (including telephone call logs, copies of registered letters and registered letter receipts) must be documented and maintained with the subject's study source documentation.

3.7 Adverse Events

3.7.1 Recording Adverse Events

If adverse events (AEs) occur, the first concern will be the welfare of the subject, including any treatment the Investigator believes is appropriate.

Adverse events that occur during the trial whether they are device related or not, will be documented. An adverse event is defined as any **clinically significant** new or changed untoward condition, or a condition requiring treatment, either surgical or medical intervention.

1. Recording of all AEs shall include the AE term and assessed relationship of the event to the study device/procedure. Additionally:
    a. Recording of ocular AEs and related AEs shall include the start and resolution dates, severity, and treatment (if any).
    b. Recording of non-ocular AEs that are not related to the study treatment will be limited to documenting the start and resolution dates (if any) from subject self- reports or other avenues and no additional information will be recorded.
    c. All AEs will be documented on the AE CRF.
2. Postoperative inflammation within or at 30 days post-surgery will be reported as an AE for cells and flare graded as 3+ or 4+.
3. Ocular events occurring greater than 30 days postoperatively that meet the following criteria will be reported as AEs.
    a. For evaluations for which a standard grading scale is available, ocular AEs will be captured for significant (2-grade) worsening.
    b. For evaluations where a standard grading scale is not available, clinically significant events assessed as mild, moderate, or severe will be captured as AEs.
4. For related, systemic AEs or all ophthalmic AEs treated with surgical intervention, the intervention should be recorded in the Ocular Procedure Log as a treatment for the AE, and the interventional treatment will not be recorded as a separate AE. If a single condition results in multiple protocol defined AE's, the root cause AE will be recorded, and the other events will be recorded as sequelae. (For example, an increase in crystalline lens opacity of greater than 3 half step increments that leads to a VF Mean Deviation loss of greater than 2.5dB. The crystalline lens opacity is recorded as an AE, and the VF Mean Deviation loss is recorded as a sequela).
5. The severity (intensity) of AEs will be rated as follows:
    a. **Mild:** subject has no, transient, or mild discomfort (< 48 hours); signs and symptoms are transient; symptoms do not interfere with the subject's daily activities; symptoms do not require medication or a medical evaluation.
    b. **Moderate:** subject has moderate discomfort; signs and symptoms are persistent; subject has some limitation in activity, or some assistance may be needed; symptoms may require no treatment or minimal medical intervention/therapy.
    c. **Severe:** subject has marked limitation in activity; signs and symptoms are persistent; symptoms interrupt participant's usual daily activity and may require medical intervention/therapy or surgery.

6. Adverse Events will be assessed by the PI for relatedness to the device / procedure. The relatedness will be determined to be:

    a. **Definitely Unrelated**: The cause of the AE is in no way related to any aspect of the study procedure, device, or study testing.

    b. **Unlikely Related:** The adverse event is unlikely to be related to the study procedure, device, or study testing, and other more likely causes are present. Relatedness cannot be ruled out with certainty.

    c. **Possibly Related:** An AE is possibly related when there is a reasonable possibility that the event might have been caused by the study procedure, device, or study testing. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.

    d. **Probably Related:** An AE is probably related when there is a reasonable possibility that the event is likely to have been caused by the study procedure, device, or study testing. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.

    e. **Definitely Related:** An AE is definitely related to study participation if the event was caused by the study procedure, device, or study testing. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.

    Throughout the course of the study, all efforts will be made to remain alert to possible adverse experiences or untoward findings.

3.7.2 Adverse events knowing to occur during or after laser procedures

Specific examples of adverse events that potentially may occur during or after laser surgery (regardless of likelihood) include but are not limited to:

- Choroidal hemorrhage
- Choroidal effusion
- Cyclodialysis cleft
- Significant hyphema (i.e. ≥ 10% of anterior chamber)
- Significant iris damage

Possible postoperative adverse events:

- Allergic reaction
- Intraocular inflammation (not pre-existing) remaining or arising after the protocol's specified medication regimen is complete
- Choroidal effusion
- Choroidal hemorrhage
- Aqueous misdirection
- Chronic pain in the study eye present greater than 3 months postoperative
- Clinically significant cystoid macular edema

- Corneal abrasion
- Flat or shallow anterior chamber (e.g., shallowing of the anterior chamber that causes any amount of iris-cornea touch)
- Hypotony (IOP < 6 mmHg) associated with clinically significant findings. (Clinically significant hypotony is defined as hypotony maculopathy or hypotony with flat anterior chamber requiring reformation, corneal folds, choroidal effusions requiring drainage, and/or suprachoroidal hemorrhage)
- Increase in C/D ratio of > 0.3 units
- IOP increase requiring management with oral or intravenous medications or with surgical intervention
- IOP increase ≥ 10 mmHg vs. baseline IOP occurring at any visit
- Iridodialysis
- Loss of best spectacle corrected visual acuity (BSCVA) of 2 lines or more (logMAR scale; 10 letters or more on ETDRS chart)
- Pupillary block
- Secondary surgical intervention
- Significant corneal complications including opacification and decompensation
- Significant corneal edema (NOTE: A classification of mild to moderate corneal edema up to and including the Week 1 postoperative exam is NOT considered an adverse event)
- Significant hyphema (≥ 10% of anterior chamber)
- Vitreous hemorrhage
- Worsening in visual field of mean deviation (MD) of ≥ 2.5 dB compared to the MD used to determine subject eligibility (confirmed in at least 2 out of 3 postoperative visual field tests performed within a 90-day period)

3.7.3 Serious Adverse Events (SAES)

Serious adverse events are defined as any findings that suggest a significant hazard, contraindication, side effect, or precaution. Any adverse event is considered a serious adverse event if it results in any of the following outcomes:

- Death
- Life- or sight-threatening
- Overnight hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

The terms “mild,” “moderate”, and “severe” are measures of intensity; thus, a severe AE is not necessarily serious. For example, nausea of several hours duration may be rated as severe but may not be clinically serious.

Important medical events that may not result in death, be life-threatening, or require overnight hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. A life-threatening event is any event that places the subject at immediate risk of death from the event as it occurred; it does not refer to an event that hypothetically might have caused death if it were more severe. A sight- threatening event is any event that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event.

Serious, alarming, and/or unusual adverse events must be reported to ViaLase within 24 hours of the investigator's knowledge of the event:

Phone: +1 (949) 466-3928

Fax: +1 (949) 900-2090

Email: clinical@vialase.com

An AE Form and supplemental SAE Report Forms must be completed as much as possible for all serious adverse events and faxed to ViaLase within 24 hours of knowledge of the event.

When new significant information (including the outcome of the event) is obtained, the investigator should inform ViaLase by telephone, facsimile, or email as soon as possible. Depending on the nature and seriousness of the AE, ViaLase may request copies of the ophthalmic and medical record of the subject as well as results of laboratory tests. If the subject was hospitalized, a copy of the discharge summary must be forwarded to ViaLase as soon as possible.

Sight-threatening AEs include but are not limited to events such as endophthalmitis and corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment, and aqueous misdirection.

Sight-threatening AEs will be reported to ViaLase and to the Investigator's IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event. Subjects who are terminated from the study due to adverse experiences will be followed until their medical outcome is determined; written reports will be provided to the ViaLase Clinical Research Department by the Investigator.

3.7.4 Unanticipated Adverse Device Effect

Unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Date and time of the event, its severity, treatment if any, and the assessed relationship of the event to the study device will be recorded on the AE form.

Unanticipated adverse device effects must be reported to ViaLase and to the Investigator's IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event. Subjects who are exited from the study due to unanticipated adverse device effects will be followed until their medical outcome is determined; the Investigator must provide written reports to the ViaLase Study Manager.

3.7.5 Follow-up after Adverse Events

Related systemic and all ophthalmic AEs for either eye at any level of potential relatedness (unlikely related, possibly related, probably related, or definitely related) will be followed and documented until complete resolution, resolution with sequelae, until the subject exits from the study for conditions with no possibility of resolution (e.g., iris atrophy, macular degeneration), or for one month after study exit.

Subjects with AEs will continue to be followed according to the protocol, unless continuing to do so would place the subject at undue risk (e.g., if they are hospitalized).

If a subject requires additional glaucoma surgery, the subject will continue to be seen for the duration of the study at required follow-up visits so that safety and effectiveness can continue to be monitored.

3.8 Source Documentation and Data Reporting

A Case Report Form booklet will be provided by ViaLase for each subject enrolled in the study. The appropriate Case Report Form will be completed at each examination. The original forms, not copies, will be returned to the sponsor along with an affidavit of obtaining signed Informed consent. Copies will be retained by the site.

ViaLase personnel will monitor all clinical studies in a manner consistent with applicable health authority regulations and the clinical research standards adopted by ViaLase, Inc.

3.9 Statistical Methods

Descriptive statistics will be used for reporting available study results. Baseline and demographic characteristics will be presented. Continuous variables will be summarized by descriptive statistics such as mean, standard deviation, median, minimum, and maximum. Discrete variables will be summarized by frequency tables and percentages.

Adverse events will be summarized by presenting the number and percentage of patients experiencing any adverse event. Any other information collected such as seriousness, severity, and relationship to study device and procedure will be listed as appropriate.

IOP change from baseline will be summarized at each evaluation by mean, standard deviation, and range. Changes in IOP from baseline (Day 0 prior to assigned treatment) will be summarized at each visit. The proportion of subjects with an IOP reduction of 20% or more from baseline will be tallied at each post-operative visit. The number and frequency of medications will be tallied at each visit.

Slit lamp exam and fundus exam findings will be summarized at each visit using frequency and percentage.

3.10 Study Monitoring

Data will be monitored according to the study data monitoring plan which includes 100% source document verification (SDV). Conduct of the investigation will be done in compliance with the currently approved protocol version, with GCP, and with Ethics Committee requirements.

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APPENDIX A – SCHEDULE OF VISITS AND CLINICAL ASSESSMENTS

Table B – Table of Scheduled Visits and Clinical Assessments

Visit Windows	Screening	Baseline	Operative Day 0	Day 1	Week 1	Month 1	Month 3	Month 6	Month 12
Window Range	1-30 days before Baseline	3-60 days before Operative	3-60 days after Baseline	1-day post-op	5-9 days post-op	21-35 days post-op	70-105 days post-op	168-196 days post-op	330-420 days post-op
Informed Consent	X								
Demographics	X								
Ocular History	X								
Ocular Medication Assessment	X	X		X	X	X	X	X	X
Medical History	X								
Medication Assessment	X	X		X	X	X	X	X	X
Pinhole VA (Snellen)				X	X				
Corrected VA (CVA)	X[1]			X	X	X[2]	X[2]	X[2]	X
Manifest Refraction		X							X
Best Spectacle Corrected VA (ETDRS)		X							X
Endothelial Cell Density		X				X		X	X
Slit Lamp Exam[3]	X			X	X	X	X	X	X

[1] Snellen chart will be used for assessing corrected VA at the Screening visit.
[2] ETDRS chart will be used for assessing corrected VA at Months 1, 3 and 6. If corrected VA indicates a greater than or equal to 10 letter loss from screening, a refraction should be performed followed by a best spectacle corrected VA assessment using an ETDRS chart.
[3] Slit lamp exam includes lenticular opacity grading.

Visit Windows	Screening	Baseline	Operative Day 0	Day 1	Week 1	Month 1	Month 3	Month 6	Month 12
Window Range	1-30 days before Baseline	3-60 days before Operative	3-60 days after Baseline	1-day post-op	5-9 days post-op	21-35 days post-op	70-105 days post-op	168-196 days post-op	330-420 days post-op
IOP via Goldmann Applanation Tonometry	X		X[4]	X	X	X	X	X	
Diurnal IOP via Goldmann Applanation Tonometry (8:00 am, 12:00pm, and 4:00 pm)		X					X		X
Gonioscopy	X				X	X	X	X	X
Dilated Fundus Exam[5]	X					X	X	X	X
Visual Field[6]		X					X	X	
Pachymetry	X							X	X
Ocular Biometry	X								
Surgery			X						
Adverse Event Assessment	X	X	X	X	X	X	X	X	
Exit									X

[4] IOP will be assessed after surgery on Day 0 and can be done at any time per investigator discretion
[5] Includes vertical C/D ratio assessment.
[6] Subjects with a visual acuity at screening of 20/100 or worst are not required to have a visual field performed.

APPENDIX B – METHODS OF CLINICAL EVALUATION

B.1 Corrected Visual Acuity

Corrected visual acuity (CVA) using either a Snellen chart or ETDRS chart will be performed at specified visits according to Appendix A.

B.2 Manifest Refraction and Best Spectacle Corrected Visual Acuity (ETDRS)

Manifest refraction (MR) and Best Spectacle Corrected Visual Acuity (BSCVA) will be performed at specified visits according to Appendix A. MR will be conducted utilizing the site's standard refractive techniques. MR must be performed prior to BSCVA testing. BSCVA testing should precede slit lamp examination, intraocular pressure measurement, the administration of topical anesthetic agents, or any examination requiring contact with the eye.

BSCVA will be assessed using the Early Treatment of Diabetic Retinopathy study (ETDRS) charts at 4 meters (13 feet and 1.5 inches, or 157.5 inches) by trained technicians. ETDRS visual acuity will be performed at specified visits according to Appendix A. BSCVA using ETDRS Chart 1 (right eye) or Chart 2 (left eye) at 4 meters will be performed at Baseline and the Month 6 visits. Corrected visual acuity (CVA) with the subject's habitual correction will be assessed using the ETDRS chart at 4 meters. If the CVA indicates a greater than or equal to 10 letter loss from baseline, then a refraction will be performed followed by a BSCVA assessment using the BSCVA method.

The ETDRS visual acuity chart may be either retro-illuminated ("back-lit"), or reflectance illuminated. If the latter, then the illumination must be checked at regular intervals to be consistent with ETDRS guidelines. The standard chart requires a distance from subject to chart of 4 meters. Ideally, the subject should be seated. Sites are directed to refer to the instructions on the commercial ETDRS charts.

The subject should attempt to read each letter, line by line, left to right, beginning with line 1 at the top of the chart (20/200 line) or a line in which they can comfortably read all the letters. The subjects should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subjects should be asked to read slowly, about one letter per second, to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response. To provide standardized and well-controlled assessment of visual acuity during the study, all visual acuity assessments for a subject must be performed consistently (e.g., the same lighting conditions, viewing distance, etc.) during the entire study. Refer to the study manual for further instruction on assessing ETDRS visual acuity.

NOTE: The study coordinator or technician can perform refractions and ETDRS visual acuity assessments if they are delegated to perform these tasks on the delegation of authority log.

B.3 Pinhole Visual Acuity (Snellen)

Pinhole visual acuity testing will be performed using an uncorrected pinhole technique using a Snellen chart at specified visits according to **Appendix A.**

B.4 Slit Lamp Exam

The slit lamp exam will be performed at the screening visit and at all postoperative visits starting with the Day 1 exam. The slit lamp exam will include the measurement of aqueous cell and flare by a standard grading system and an evaluation for the presence of corneal abnormalities, pupillary irregularities, iris atrophy and pigment dispersion.

For the evaluation of aqueous cells and flare, use the following SUN grading schemes (22):

B.4.1 Grading Scheme for Anterior Chamber Cells

Table C – Anterior Chamber Cell Grade Scheme

Grade	***Cells in Field****
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

*Field size is a 1mm by 1mm slit beam

B.4.2 Grading Scheme for Anterior Chamber Flare

Table D – Anterior Chamber Flare Grade Scheme

Grade	***Description***
0	None
1+	Faint
2+	Moderate (iris and lens detail clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

B.4.3 Grading Scheme for AREDs 2008 Clinical Lens Opacity

1. Dilate pupils to at least 5 mm diameter.
2. Use slit lamp with approximately 10X magnification.
3. Use brightest beam intensity.
4. Nuclear opacity
    a. Orient beam at 45° to viewing axis.
    b. Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width.
    c. Compare opalescence of nucleus with that in standard photos.
5. Cortical and PSC opacities
    a. Select wide slit beam setting optimum for retro-illumination of lens.
    b. Visualize lens opacities against red fundus reflex background Count only opacities visible against red reflex.
    c. Mentally combine all cortical opacities into contiguous area.
    d. Compare total opacity area with that in standard photos.
6. Classify each opacity with scale defined by 3 standard photos.
7. Select nearest half-step.

a. Similar to standard or between two standards.

b. Obviously less than mildest standard or greater than most.

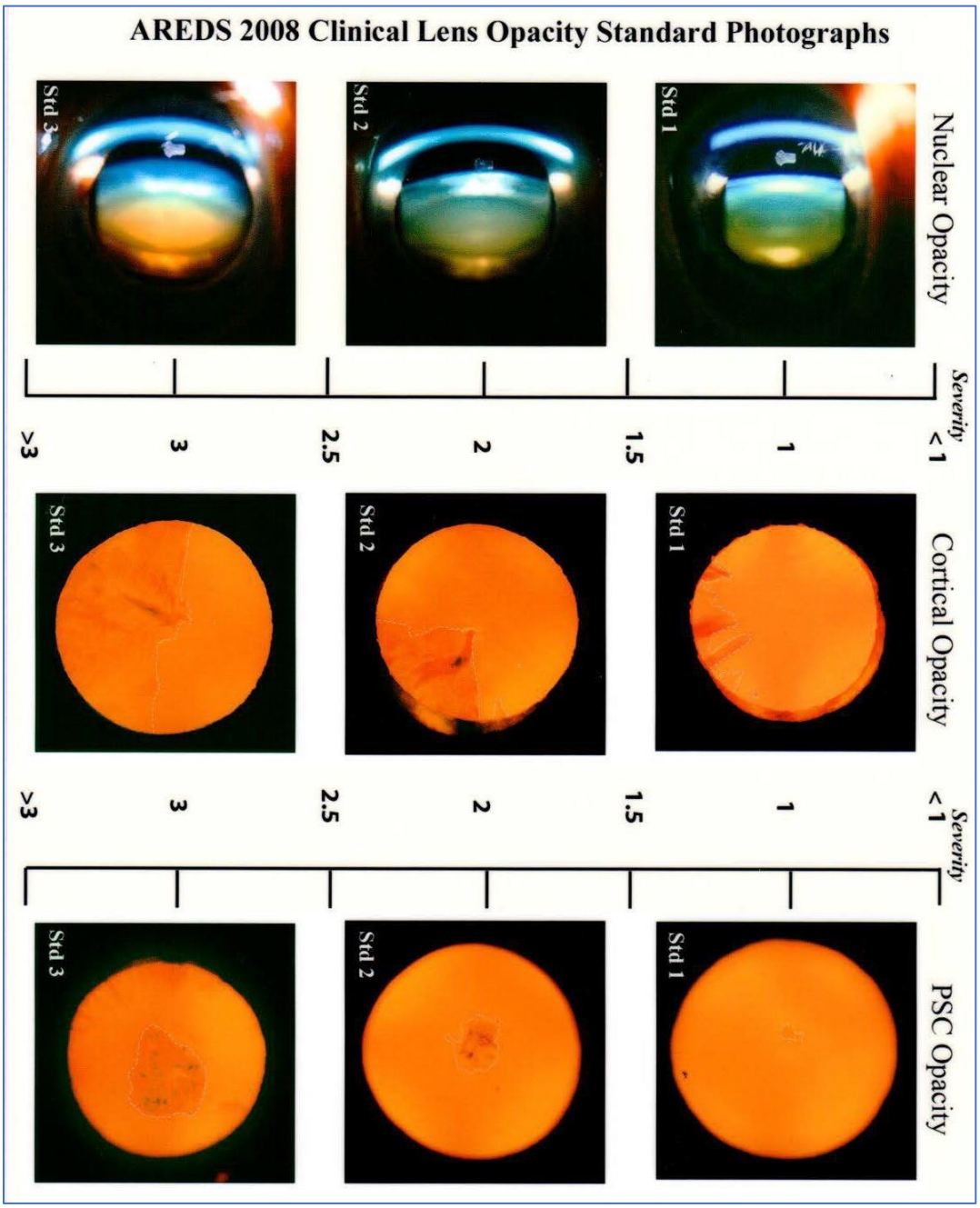

Figure 3 – AREDS 2008 Lens Opacity Standard

B.5 Applanation Tonometry

Applanation tonometry using a Goldmann tonometer will be used to measure intraocular pressure (IOP) at all visits. At each visit, IOP will be measured prior to gonioscopy or dilation of the pupil. Subjects should be instructed to take their medication(s), if any, as usual the day of the visit.

IOP will be measured by 2 observers. Observer 1 (masked to real time IOP reading) will look through the slit lamp and turn the dial, with Observer 2 using the sponsor supplied IOP dial view blocking card and associated procedure. Observer 2 will read the result from the Goldmann tonographer knob and record the IOP readings.

At each IOP timepoint measurement, two measurements will be taken, and the mean recorded on the case report form unless they differ by more than 2 mmHg, in which case a third measurement is taken and the mean is computed.

Tonometer calibration for all study tonometers used in the study must be performed monthly and documented in the calibration log in the study regulatory binder.

B.6 Gonioscopy

Gonioscopy will be performed on all subjects and will be used to assess angle abnormalities including presence of goniosynechiae, angle anatomy and stent location (post-implantation). Please refer to Appendix A. At the screening exam, the Shaffer system for grading the angle anatomy will be used as follows:

B.6.1 Gonioscopic Angle Grade

Table E – Gonioscope Angle Grade Scheme

Angle - θ	***Grade***
$0° \leq \theta < 10°$	Closed
$10° \leq \theta < 15°$	I
$15° \leq \theta < 25°$	II
$25° \leq \theta < 35°$	III
$\geq 35°$	IV

B.7 Visual Field Examination

Screening visual fields are used to determine subject eligibility prior to enrollment into the study, and as safety measures through the course of the study. For subjects with a screening visual acuity of 20/100 or worse, a visual field is not required at screening.

Visual fields must be automated threshold visual fields using Humphrey 24-2, SITA Standard. This program will be used for the duration of the study at the required visits (refer to Appendix A). Visual field testing can be performed dilated or undilated if the method is consistent at each visit. There are no restrictions on how to prepare subject's eyes for the visual field exam. NOTE: Visual field exams conducted ≤ 3 months of the screening visit can be used as part of the subject's evaluation for inclusion in (or exclusion from) the study as long as the test is performed with Humphrey 24-2, SITA Standard methodology. Values for mean deviation will be recorded.

B.8 Pachymetry

Pachymetry is performed to determine central corneal thickness. For each evaluation, three measurements (or sequential independent measurement sessions for instruments that automatically take multiple readings from one corneal touch) are to be taken utilizing an ultrasonic pachymeter and the mean recorded. There are no restrictions on the type of pachymeter usedin collection of data for this study. For those pachymeters that are not self-calibrating, calibration must be performed on a quarterly basis and documented in the calibration log in the study regulatory binder.

B.9 Endothelial Cell Density

Specular microscopy for endothelial cell density will be performed in all subjects. Specular microscopic images will be taken at Screening, 1-month, 6 month, and 12-month visits. These images will be taken at the central corneal position of both eyes. Endothelial cell density, percent hexagonality and the coefficient of variation will be assessed from specular microscope images. Images will be stored on the computer hard drive and copied onto recordable media. Media will be labeled with the protocol number, investigator number, subject number, image date, visit number.

B.10 Biometric Data

Upon availability of an eye mapping device, the following biometric data may be collected at baseline: the temporal to nasal white-to-white diameter of anterior chamber depth; the anterior corneal radius of curvature; the posterior corneal radius of curvature; and the anterior chamber depth.

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APPENDIX D – SPONSOR'S COMMITMENTS

ViaLase, Inc. is committed to:

1. Complying with the Declaration of Helsinki, and all applicable health authority regulations governing the conduct of clinical research studies.
2. Protecting the rights, health, safety, and welfare of study subjects.
3. Informing the clinical Investigators of any new information about the study which may affect the health, safety, or welfare of the subjects, or may influence their decision to continue participation in the study.
4. Providing the clinical Investigators with the study protocol, and a full set of Case Report Forms on which to document the study evaluation variables for each subject entered the study.
5. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.
6. Ensuring equity of consideration among all Investigators in multicenter studies in all matters of publications, meeting presentations, etc.
7. Certifying that IRB approval of the protocol and Investigators Agreement will be completed prior to treatment at an investigational site.

APPENDIX E – INVESTIGATOR'S QUALIFICATIONS AND RESPONSIBILITIES

Each Investigator must be a licensed physician who has completed a residency or preceptorship in ophthalmology. The Investigators have the following responsibilities:

E.1 Subject Selection

The Investigator is responsible for assuring that all subjects entering the study conform to the subject selection criteria.

E.2 Informed Consent

The Investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with prospective subjects prior to their enrollment in the study. The Investigator is responsible for obtaining written Informed Consent in compliance with 21CFR 50 for each subject, prior to enrollment in the trial. A copy of the signed Informed Consent Form will be maintained in the subject's medical record or research chart, and a copy of the signed Informed Consent Form will become an integral part of each Case Report file provided to the Sponsor.

E.3 Institutional Review Board (IRB) Approval

The Investigator must obtain approval for participation in this protocol from the IRB for the institution at which the procedure will be performed, prior to entering any subjects in the study. The Informed Consent document to be used will also be submitted by the Investigator to the IRB for approval prior to initiation of the study. Assurance that the IRB approval of the study protocol and Informed Consent has been obtained will be provided to the Sponsor prior to initiation of the study.

E.4 Subject Evaluations and Data Reporting

The Investigator is responsible for performing all subject evaluations as described in the study protocol. All information generated by the subject evaluation will be recorded on the Subject Case Report Forms provided by the Sponsor. The Investigator is responsible for working with their staff and study subjects to provide all study data requested because missing data could jeopardize the integrity and scientific value of the study. Case Report Forms will be filled out in ink. Any corrections will be made by lining out with initials and date. Correction fluid will not be used. The Investigator will sign and date each set of forms upon its completion and will return the originals, not copies, to ViaLase. Copies of all Case Report Forms will be retained in the Investigator's office to be available for monitoring by ViaLase personnel or by authorized FDA personnel.

Following completion of each subject examination the completed, signed and dated Subject Case Report Form shall be collected by the Sponsor in a timely manner for review and statistical analysis.

Investigator(s) will not deviate from the study protocol without prior approval of ViaLase unless protection of the health, safety or welfare of study subjects requires prompt action.

E.5 Record Retention

The Investigator shall maintain all subject records for whichever of the following periods is shortest:

1. A period of two years after the date on which the FDA approves the marketing of the device for the purpose that was the subject of the study.
2. A period of five years after the date on which the results of the study are submitted to the FDA in support of the marketing of the device for the purpose that was the subject of the study.

APPENDIX F – DECLARATION OF HELSINKI

Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

Publication Date, October 2013

F.1 PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

> The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

F.2 GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being, and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures, and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training, and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

F.3 RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed, and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

F.4 Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

F.5 Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

F.6 Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

F.7 Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

F.8 Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

> After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
>
> All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed,

the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

F.9 Use of Placebo

33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

F.10 Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

F.11 Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research

not in accordance with the principles of this Declaration should not be accepted for publication.

F.12 Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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