PROTOCOL VIS-2014

A PROSPECTIVE, MULTICENTER CLINICAL TRIAL OF
THE VISABILITY IMPLANT SYSTEM
FOR IMPROVEMENT OF NEAR VISUAL ACUITY IN PRESBYOPIC PATIENTS

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Date of Protocol: October 13, 2014
Date of Protocol Amendment 2: March 3, 2015

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

_____
Print Name of Investigator

_____ _____
Investigators' Signature Date

PROTOCOL VIS-2014
TABLE OF CONTENTS

1.0 PERSONNEL AND FACILITIES

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2.0 ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ASI	Anterior Segment Ischemia
BCDVA	Best Corrected Distance Visual Acuity
BCNVA	Best Corrected Near Visual Acuity
BSS	Balanced Salt Solution
CPS	Critical Print Size
CRF	Case Report Form
CRO	Clinical Research Organization
CRSE	Cycloplegic Refraction Spherical Equivalent
CSLO	Confocal Scanning Laser Ophthalmology
dB	Decibel
DCNVA	Distance Corrected Near Visual Acuity
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICC	Intraclass Correlation Coefficient
ICD	International Classification of Diseases
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
LASIK	Laser Assisted In-Situ Keratomileusis
LogMAR	Logarithm of the Minimum Angle of Resolution
LST	Lamellar Scleral Tunnel
MD	Mean Deviation
mm	millimeters
mm Hg	Millimeters of Mercury
MRSE	Manifest Refraction Spherical Equivalent
NAVQ	Near Acuity Visual Questionnaire
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCT	Optical Coherence Tomography
OD	Right Eye
OS	Left Eye
PG	Prostaglandin
PI	Principal Investigator
PMA	Premarket Approval
PMMA	Polymethylmethacrylate
PRO	Patient Reported Outcomes
PSD	Pattern Standard Deviation
PSI	PresVIEW Scleral Implants
PTFE	Polytetrafluoroethylene
SAE	Serious Adverse Event
SITA	Swedish Interactive Threshold Algorithm
SOP	Standard Operating Procedure
SPK	Superficial Punctuate Keratitis

UADE	Unanticipated Adverse Device Effect
UBM	Ultrasound Biomicroscopy
UCDVA	Uncorrected Distance Visual Acuity
UCIVA	Uncorrected Intermediate Visual Acuity
UCNVA	Uncorrected Near Visual Acuity
UK	United Kingdom
US	United States
VIS	VisAbility Implant
VIS	VisAbility Implant System
VR-QOL	Vision Related Quality of Life

3.0 STUDY SYNOPSIS

The objective of this study is to evaluate the safety and effectiveness of the VisAbility Implant System (VIS) for the improvement of near visual acuity in presbyopic patients. This is a prospective clinical study that will enroll and determine eligible a total of 360 subjects ranging in age between 45 and 60 years of age at up to 14 clinical sites. Subjects will be implanted with the VisAbility Implant [redacted] in the primary eye and then in the fellow eye no sooner than 14 days later. Subjects will be examined at one day, one week and at 1, 2, 3, 6, 12, 18 and 24 months post-operatively.

The study will also include a 60 subject randomized controlled sub-study at 3 investigational sites. Subjects enrolled and eligible at these sites will be randomized (1:1 ratio) to a surgery group or a control group. Subjects randomized to the surgery group will undergo surgery and will be followed for 24 months in the same manner as the larger non-randomized surgical group. Subjects randomized to the control group will be followed for 6 months, and will be eligible to undergo surgery after completion of this 6-month follow-up period.

The primary endpoint is achievement of distance corrected near visual acuity (DCNVA) of Snellen equivalent 20/40 or better (at 40 cm) and at least 10 letters (ETDRS) improvement in DCNVA in the primary eye.

This endpoint will be evaluated against two objectives, a) 75% or more of primary eyes achieve the effectiveness endpoint at 12 months postoperative and b) the percentage of primary eyes achieving the effectiveness endpoint at 6 months postoperative (6-month responder rate) is higher than the percentage in the randomized control group.

A PMA application will be submitted when the full study cohort has completed the 12 month follow-up visit.

4.0 BACKGROUND AND REGUALORY CHRONOLOGY

4.1 Background

Clinical evaluation of PresVIEW Scleral Implants (PSI) was initiated in 1997 following FDA approval of G970152. The initial clinical trial was a feasibility study in presbyopic subjects desiring improvement in near visual acuity. Based on the encouraging outcomes of the feasibility study a large clinical trial of the PSI was initiated in 2003 under Protocol P-277-5, and two models of the PSI have been evaluated.

The PSI [redacted] was implanted in 164 subjects (213 eyes) from 1999 through 2007. The PSI [redacted] was introduced in 2009 to provide better fixation of the PSI in the scleral tunnel. Since there were significant differences in the design of the PSI [redacted] and [redacted], a full cohort of 330 subjects (645 eyes) was implanted [redacted].

Both scleral implant models [redacted] and [redacted] consist of four segments which are implanted in scleral tunnels in the four oblique quadrants of the eye. From 1999 through 2000, scleral tunnels were created using a diamond blade. An automated, electrically powered, re-usable device designed specifically for scleral tunnel creation, called the Scleratome, was introduced in 2003 and this incision system was used through mid-2012. In April 2012, FDA approved introduction of a smaller, lighter, disposable Scleratome into the ongoing IDE clinical trial. Since the tunnel configuration was the same for both Scleratomes, as demonstrated in performance testing submitted in the IDE supplement supporting introduction of the disposable Scleratome, Refocus assumed that clinical data from both the re-usable and the disposable Scleratome were expected to be comparable.

After introduction of the disposable Scleratome in May 2012, 56 subjects (119 eyes) were implanted in incisions made with this improved Scleratome. An exploratory analysis of 12 month clinical outcomes of these eyes as compared to eyes implanted with the earlier reusable Scleratome provided evidence of greater improvements in near vision with the disposable Scleratome. While this finding was unanticipated, it was also very encouraging since these improvements in near vision were achieved considerably earlier in the postoperative period.

This finding was also important since it confirmed Refocus' expectation that improved surgical instrumentation would have a favorable effect on postoperative clinical outcomes, as evidenced in the transition from the original IDE pilot study in which scleral tunnels were created using a diamond blade to use of the automated, re-usable Scleratome introduced in 2003 and to the more recent introduction of the disposable Scleratome.

In Protocol P-277-5, conducted under G970152, the location of the scleral incisions for placement of the PSI was identified by marking the targeted position of the incisions. This method was not completely reliable since the marking can be difficult for the surgeon to see during the procedure. As a result, some surgeons had experienced difficulty placing the Scleratome in the proper position relative to the marks created.

4.2 Rationale for Protocol VIS-2014

In a further effort to develop improved surgical instrumentation that would provide more reliable placement of the scleral tunnels created by the Scleratome, the company has developed an integrated surgical instrumentation system, called the VisAbility Implant System.

[redacted]

Given the potential for the VisAbility Implant System to improve results of the implantation procedure, Protocol VIS-2014, a new pivotal trial, is being conducted to definitively evaluate the safety and effectiveness of the VisAbility Implant System.

5.0 SCIENTIFIC BACKGROUND ON PRESBYOPIA

Presbyopia is the most prevalent of all visual deficiencies, affecting virtually 100% of the population over the course of a normal life span. It is characterized by a progressive, age-related loss of accommodation, or the ability of the human eye to focus clearly on objects over a range of near to intermediate distances from the eye. By the fifth decade of life, the amplitude of accommodation has declined so that the near point of the eye is more remote than typical reading distance. Once presbyopia occurs, emmetropes will need an optical aid for near vision. Myopes will find they see better at near without their distance correction and hyperopes will require a correction for both distance and near vision.

When the eye accommodates to focus on a near object, convergence and pupil constriction also occur. The combination of these three movements (accommodation, convergence and miosis) is under the control of the Edinger-Westphal nucleus and is referred to as the near triad, or accommodation reflex. Accommodation is accomplished by the ability of the human eye to alter the refraction of the crystalline lens, depending on the distance of the object from the eye. In the eye of a presbyopic emmetrope, the lens cannot accommodate sufficiently to focus the light rays from a near object onto a single point on the retina. Thus, a point object is imaged as a blur circle on the retina. Loss of accommodation typically begins in mid-life, eventually culminating in a nearly complete loss of the ability of the eye to clearly visualize near objects.

Currently, no universally accepted surgical treatments are available for presbyopia. Vision correction options include near vision reading glasses and/or contact lenses. As the physiological mechanisms of accommodation are investigated, more therapeutic and corrective options are being explored. These include the use of multifocal intraocular lenses (IOLs), monovision and anisometropic corneal refractive surgical procedures using laser-assisted in situ keratomileusis (LASIK), corneal implant devices, and the VisAbility Implant.

5.1 Lenticular and Extralenticular Theories

The underlying cause(s) of presbyopia, loss of accommodation of the eye over time, is not completely understood or agreed upon by the medical community. Scientific theories for accommodative loss may be generally ascribed to two schools of thought:

- Lenticular Theories are broadly based on age-related changes in properties of the lens of the eye, including the lens substance, the lens capsule, and the zonular fibers. These theories stem not only from purported changes in the elasticity of the tissues, but also from continued growth and changes in the thickness and the curvature of the lens with age. Helmholtz's lenticular theory of the loss of accommodation is the most widely accepted of these types of theories.[1] The majority of current approaches for the treatment of presbyopia are based upon lenticular theories of accommodation.

- Extralenticular Theories consider age-related changes in the accommodative structures outside of the lens, capsule, and zonules. These factors include anatomical, morphological, and physiological changes in the ciliary muscle, connective tissue, and choroid. The Scleral Implant approach to the treatment of presbyopia is based on extralenticular theories.

5.2 Theories of Accommodation

For the past 150 years, Helmholtz's lenticular theory of the loss of accommodation has been the accepted basis for the underlying physiological mechanisms that lead to presbyopia[1] Helmholtz hypothesized that presbyopia is caused by the hardening of the lens with age. According to Helmholtz, as the ciliary body contracts for accommodation, it constricts inwardly and relaxes the zonules. The relaxation of the zonules causes the lens to "round up", and as the lens becomes more convex, it adds dioptric power thus bringing near objects into focus. According to Helmholtz's theory, the decrease in flexibility of the lens and the loss in elasticity of the lens capsule that occur with aging progressively hinder the focusing mechanism.

Although generally accepted, Helmholtz's theory cannot fully explain the mechanism by which the lens alters its shape, nor can it satisfactorily explain the reason or means by which aging uniformly affects accommodation across the population.

An extralenticular theory that may explain age-related changes in accommodation is Dr. Jackson Coleman's catenary theory of accommodation.[2,3,4] Coleman's theory proposes that the lens, zonules, and anterior vitreous comprise a diaphragm between the anterior and vitreous chambers of the eye. According to Coleman, this construct behaves in a manner analogous to a hydraulic suspension bridge, or catenary**.** When the ciliary muscles contract to accommodate the lens, pressure is increased in the vitreous compartment.

Simultaneously, pressure in the anterior chamber is decreased due to the expansion of the trabecular meshwork, which occurs with ciliary body contraction. A pressure gradient is thus established between the 2 chambers, resulting in a posterior flattening of the lens and, anteriorly, in a steeper radius of curvature in the center of the lens with a slight flattening at the periphery.[6]

The anterior capsule and the zonules form a hammock-shaped surface (a modified catenary) that can be predicted mathematically based on the circumference of the ciliary body (Müeller's muscle).[7] Much like the pylons of a suspension bridge, the ciliary body dictates the shape of the catenary. Thus, the accommodated state appears to be supported by the fluid volume differential with very little energy expenditure, much like a viscose-damped hydraulic door closer.

Coleman's hypothesis has been tested by comparing a mechanical model of accommodation with *in vivo* measurements of lens geometry changes during accommodation (measurements included ultrasound, MRI, and optical techniques).[6,7,8] The mechanical model consisted of fluid-filled latex balloons which were supported by a plastic wrap hammock to form a curve that potentially models the human lens. Increasing balloon volumes were used to simulate growth of the aging lens, and variations in curvature were measured.

Schachar proposed an alternative extralenticular theory. He hypothesized that presbyopia is a result of a decrease in distance between the ciliary muscles and lens equator. It is known that lens tissue continues to grow over the lifetime of an individual,[8] while sclera stops growing at approximately age 13.[10] Therefore, there is a linear decrease in the distance between the ciliary muscles and the lens over time. Ciliary muscles are smooth with striations, and thus, the amount of tension they can develop is directly related to the degree to which they are stretched. Over time, the amplitude of accommodation is reduced because the distance between the lens and the muscles is decreased, resulting in presbyopia. Stretching the ciliary muscles by surgical intervention would increase their ability to exert force on the lens and improve near vision.

More recently, Goldberg and colleagues have made efforts to incorporate the research findings of others in a computer-animated model of accommodation[11]. Dr. Goldberg notes that, "*A team of European investigators (Elke Lutjen-Drecoll, MD, and colleagues at the Institute of Anatomy in Erlangen, Germany) and American investigators (Mary Ann Croft, MS; Paul Kaufman, MD; and colleagues at the National Primate Lab and University of Wisconsin in Madison) have used electron microscopy and video ultrasound biomicroscopy (UBM) and endoscopy to define the complex, separate elements of the zonules and document the interconnected movements of the extralenticular tissues.*" Dr. Goldberg suggests that the mechanism of accommodation should include a new theory of reciprocal zonular action, which he describes as follows: "*During ciliary body contraction, the anterior zonules lose tension while the posterior zonules stretch. During ciliary body relaxation, the posterior zonules lose tension as the lens flattens and is pulled back by the increasing tension of the anterior zonules*."

The exact cause of the loss of accommodation over time is not known and may be associated with the above theories, a combination of these theories, or theories not yet introduced.

6.0 PRIOR SCLERAL IMPLANT CLINICAL STUDIES

As briefly described in the introduction to this protocol, Refocus has conducted a feasibility study of the scleral implants in 29 presbyopic subjects, followed by a pivotal trial that enrolled 135 subjects with the [redacted] design of the PresVIEW Scleral Implant and 330 subjects [redacted]. The results of these studies are described briefly below.

6.1 Feasibility Clinical Study

Clinical evaluation of the scleral implants was initiated in March 1999 following FDA approval of G970152. The feasibility clinical trial enrolled 29 presbyopic subjects desiring improvement in near visual acuity at 6 clinical sites. Subjects were implanted in the primary eye only and followed for 24 months. Four PMMA segments were implanted in partial thickness scleral tunnels in the four oblique quadrants of the eye. The scleral tunnels were made using a diamond blade.

While some study subjects experienced a clinically significant improvement in near visual acuity in this study, the effectiveness results were mixed as a result of difficulty in accurately and consistently creating the scleral tunnels. Notwithstanding these challenges, the initial results provided evidence of safety and effectiveness and supported initiation of a larger clinical trial. Importantly, the findings regarding difficulty in scleral tunnel creation led to development of an automated, electrically powered, re-usable incision device, the Scleratome, which was used in subsequent clinical studies.

6.2 Pivotal Trial of the [redacted] Scleral Implant (Protocol P-277-5)

A prospective, randomized controlled multicenter clinical trial of the [redacted] scleral implant was approved by FDA in December 2003. Subjects were implanted with the [redacted] and followed for 24 months. In the initial randomized controlled stage of this study, 150 subjects were to be randomized in a 2:1 ratio either to a surgical cohort (N=100) or to a Deferred Treatment / Control cohort (N=50) with an interim report to be provided to FDA upon obtained preliminary data on 75 randomized subjects. Subjects randomized to the deferred surgery/control cohort were eligible to receive the implant after completion of 6 months of follow-up in the study.

In the initial stage of this study, a total of 81 subjects were enrolled and randomized to either the PSI Treatment Group (53) or the Deferred Treatment Control Group (28) at a ratio of 2:1 per the study protocol. At the 3-month visit, 64% (23/36) of the eyes assigned to the PSI Treatment Group had distance corrected near visual acuity 20/40 or better, as compared with 6% (1/18) of Deferred Treatment Control Group. At the 6-month postoperative exam 70% (30/43) of the eyes in the PSI Treatment Group eyes had distance corrected near visual acuity 20/40 or better, as compared with 4% (1/23) of the Deferred Treatment Control eyes.

While these data supported expansion to the full study cohort of 330 subjects and up to 660 eyes, with bilateral implantation, only a total of 184 eyes of 135 subjects were implanted with the [redacted] under this protocol.

Initial effectiveness outcomes were consistent with the results of the initial subjects in the randomized substudy, however the improvement in near visual acuity was not sustained over time in some subjects. During investigation of this unexpected finding, imaging of the [redacted] segments using the Visante OCT (Carl Zeiss Meditec, Jena, Germany) revealed displacement of at least one of the implant segments in subjects who experienced an initial improvement in near vision followed by loss of this improvement.

Subsequently, in a group of patients with displaced segments, repositioning and suturing of the segments was associated with clear improvements in near acuity, and confirmed that the stability of the [redacted] segments in the scleral tunnel was directly related to clinical efficacy.

Since suturing of the [redacted] significantly increased procedure time and complexity, Refocus deferred further enrollment in the study pending design changes to the scleral implant segment to resolve the displacement issue. A new design was developed, which incorporated a two part implant segment; a main body with “feet” at both ends that protruded beyond the edges of the tunnel and a secondary locking insert. This design, known as the PSI [redacted], was introduced into Protocol P-277-5, and has been shown to reliably maintain the implant segment firmly in place, as described further below.

6.3 Pivotal Trial of the [redacted] Scleral Implant (continuation of Protocol P-277-5)

The PSI [redacted], designed to provide better fixation of the PSI in the scleral tunnel, was introduced into Protocol P-277-5 in June 2009. Since 135 subjects had already been enrolled and implanted with the [redacted] design, enrollment was increased to 465 subjects to ensure that 330 subjects could be enrolled and implanted with the PSI [redacted] in support of a Premarket Approval Application (PMA).

With the modified design of the PSI segment, another 48 patients were to be enrolled in a sub-study and randomized (2:1 ratio) with 32 patients receiving the PSI [redacted] and 16 deferred surgery/control patients. As before, subjects randomized to the deferred surgery/control cohort were eligible to receive the PSI after completion of 6 months of follow-up in the study. The results of patients who elected to have PSI surgery after completion of 6 months of follow-up in the deferred/control surgery group were included in the total patient cohort.

A smaller, lighter, disposable Scleratome was also introduced into the ongoing IDE clinical trial in April 2012. Since the tunnel configuration was the same for both Scleratomes, as demonstrated in performance testing, Refocus assumed that clinical data from both the re-usable and the disposable Scleratome would be comparable. However, an exploratory analysis of 12 month clinical outcomes for 56 primary eyes (119 total eyes) implanted with PSI using the disposable Scleratome showed greater improvements in near vision following surgery with this improved surgical tool as compared to earlier subjects in the cohort. While this finding was unanticipated, it was also very encouraging since the improvements in near vision were also achieved considerably earlier in the postoperative follow-up period. These findings were important since they confirmed Refocus’ expectation that improved surgical instrumentation would have a favorable impact on the post-operative clinical outcomes, as evidenced in the transition from the original IDE pilot study in which scleral tunnels were created using a diamond blade to use of the automated, re-usable Scleratome introduced in 2003 and to this more recent introduction of the disposable Scleratome.

A total of 645 eyes of 330 subjects were enrolled and implanted with the PSI [redacted] in this clinical study. Subjects implanted with the PSI [redacted] experienced clinically meaningful improvement with DCNVA (Sloan) at 40cm. DCNVA (Sloan) of 20/40 or better was achieved by 80% (237/298) of subjects at 12 months, by 84% (210/249) of subjects at 18 months and by 91% (120/132) of subjects at 24 months.

Further, during the course of this clinical trial no persistent loss in BCDVA or BCNVA was observed in any eye. BCDVA remained generally unchanged from baseline through the 24 month visit and all (100%) of the PSI treated eyes achieved BCNVA of 20/32 or better at all postoperative examinations.

The PSI [redacted] has not been modified since its introduction into the clinical trial conducted under G970152, and there are no plans to modify this model of the PSI.

Frequently reported ocular adverse events in this clinical trial were dry eye and improper conjunctival closure after the surgical procedure, the latter resulting in exposed implant segments. Exposed segments were treated with revised conjunctival closures. Other ocular adverse events included conjunctival tags, corneal abrasions, conjunctival injection, superficial punctuate keratitis (SPK), conjunctival thinning, and exposed suture. All of these were transient in nature and resolved without sequelae, generally with no or limited medical intervention. IOP increases secondary to postoperative administration of topical steroid drops were reported; in all cases, IOP returned to the baseline level after discontinuation of the steroid drops and/or short-term use of IOP lowering medications in a few cases.

Three (3) cases of decreased iris vascular perfusion resulting in decreased pupil reactivity to light, and iris atrophy were reported in the complete cohort of 858 eyes of this IDE study for an incidence of 0.35%. This adverse event has been mitigated with a high level of standardization of the immediate post-operative surgical protocol to ensure detection of any adverse change in pupil function where recovery falls below minimum standards. In those rare cases, the implant segments will be removed on the day of surgery prior to discharge, thereby reversing any decrease in iris vascular perfusion**.** All prior cases achieving a measured pupillary response of ≥ 25% constriction by digital infrared pupillometry within 6 hours post-operatively have demonstrated no long-term compromise in pupillary function, nor have they developed any further signs or symptoms of decreased perfusion. Therefore, this protocol will require removal of implant segments on the day of surgery in the rare circumstance that the pupillary constriction does not return to an acceptable level in the immediate postoperative period.

In summary, adverse events were observed in the original IDE study but these were generally mild in nature, self-limiting and largely resolved by 6 months postoperatively. The majority of the adverse events occurred during the early postoperative period, with no serious or significant adverse events observed in the late postoperative period, i.e., at 6 months or later.

7.0 STUDY OUTLINE

7.1 Study Objective

The primary objective of this study is to evaluate the safety and effectiveness of the VisAbility Implant System with the VisAbility Implant, [redacted], for improvement in distance corrected near visual acuity (DCNVA) in presbyopic subjects.

7.2 Study Design

This is a prospective multicenter clinical study that will enroll and determine eligible 360 subjects ranging in age between 45 and 60 years of age with distance corrected near visual acuity (DCNVA) and uncorrected near visual acuity (UCNVA) of 20/50 to 20/80 (inclusive). Subjects will be enrolled at up to 14 clinical sites with no site enrolling and determining eligible more than 20% of the 360 eligible subject cohort. A PMA application will be submitted when all study subjects have completed 12 months of follow-up.

Subjects will be consented and screened based on medical history, ocular history and visual acuity criteria. Subjects will be required to satisfy specific inclusion and exclusion criteria during a baseline examination to be eligible for surgery. Subjects will be implanted with the VisAbility Implant [redacted] in the dominant eye, which will be designated as the primary eye. The fellow eye will be implanted no sooner than 14 days after the primary eye and only in the absence of unresolved adverse events in the primary eye. Subjects primary eye will be examined at one day, one week and at 1, 2, 3, 6, 12, 18 and 24 months post-operatively. The fellow eye will be examined at one day, one week and one month postoperatively. The one week and one month examinations of the fellow eye may be combined with visits for the primary eye if the visit windows permit. After the fellow eye one month visit, the fellow eye will be examined in accordance with the subsequent primary eye examination visits. A validated Patient Reported Outcome Measurement instrument [redacted] will be given to all enrolled and eligible subjects pre-operatively and at 6, 12, 18 and 24 months.

The study also includes a 60 subject randomized controlled sub-study at 3 investigational sites. Eligible subjects enrolled at these sites will be randomized (1:1 ratio) to a surgery group or a control group. Subjects assigned to the randomized surgery group will be implanted and followed for 24 months in the same manner as the larger non-randomized surgery group. Subjects randomized to the control group will be followed for 6 months, and will be eligible to undergo VisAbility Implant surgery after completion of the six month observation period. These subjects that elect surgery will be followed for 24 months in accordance with the same schedule as the non-randomized surgery group. Randomized control group subjects who do not chose to undergo VisAbility Implant surgery at the end of the 6 month observation period will be exited from the study at that time.

7.3 Effectiveness Endpoint

The primary endpoint is achievement of distance corrected near visual acuity (DCNVA) of Snellen equivalent 20/40 or better (at 40 cm) and at least 10 letters (ETDRS) improvement in DCNVA in the primary eye.

This endpoint will be evaluated against two objectives, a) 75% or more of primary eyes achieve the effectiveness endpoint at 12 months postoperative and, b) the percentage of primary eyes achieving the effectiveness endpoint at 6 months postoperative (6-month responder rate) is higher than the percentage in the randomized control group.

7.4 Analysis of Safety Data

Safety data analyses will be performed and separate summaries will be provided for primary and all eyes. Descriptive statistics on the following attributes will be provided:

- BCDVA
- IOP
- Slit Lamp findings
- Fundus exam findings
- Rate of adverse events

7.5 Study Population

A total of 360 subjects who meet the following criteria will be enrolled and determined eligible in this study:

7.5.1 Inclusion Criteria

1. Subjects must be between ages of 45 to 60 at the time of enrollment.

2. Subjects must have best corrected distance visual acuity (BCDVA) of 20/20 in each eye.

3. Subjects must have distance corrected near visual acuity (DCNVA) @ 40 cm of 20/50, 20/63 or 20/80 in each eye.

4. Subjects must have uncorrected near visual acuity (UCNVA) @ 40 cm of 20/50, 20/63 or 20/80 in each eye.

5. Subjects must have preoperative manifest refraction spherical equivalent (MRSE) in each eye of -0.75 to +0.50 diopters with no more than 1.00 diopter of astigmatism. The difference between the MRSE and cycloplegic refraction spherical equivalent (CRSE) should be ≤0.50 diopter.

6. Subjects must require a minimum add of +1.25 or greater to read 20/20 at near (40 cm).

7. Subjects must be phakic in each eye.

8. Subjects must be alert, mentally competent, and able to understand and comply with the requirements of the clinical study, and be personally motivated to abide by the requirements and restrictions of the clinical study. Patients must be available for the follow-up period.

9. Subjects must be able to provide written informed consent.

7.5.2 Exclusion Criteria

1. Subjects where either pupil has a baseline percent change from scotopic to photopic of less than 30% or an absolute difference of less than 1.00 mm between scotopic and photopic pupil size as measured by the NeurOptics Pupillometer.

2. Subjects with ocular inflammation, chronic uveitis, or other recurrent anterior or posterior segment inflammatory conditions in either eye; subjects with any ocular or systemic disease(s) posting a significant risk for ocular inflammation, including but not limited to autoimmune disorders (e.g., rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, ulcerative colitis, Crohn's disease, psoriasis, sarcoidosis, Behcet's disease), infections (toxoplasmosis, cat-scratch fever, West Nile virus, syphilis, tuberculosis, herpes zoster, herpes simplex, adenovirus), ocular trauma, or gout.
3. Subjects with scleral thickness of less than 530 microns as measured 3.5 to 4.0 mm posterior to the superior temporal quadrant limbus in either eye.

4. Subjects with a history of any prior intraocular procedure (e.g., corneal transplant, filtering procedures for glaucoma, vitrectomy, retinal detachment repair, cataract surgery) or any prior refractive procedure (e.g. LASIK, surface excimer, or incisional surgery) in either eye.

5. Subjects with any history of prior extraocular muscle surgery or orbital surgery.

6. Subjects with chronic ocular disease, including but not limited to corneal pathology, primary or secondary glaucoma, iritis, herpes simplex, uveitis, trachoma, ocular pemphigoid, Sjogren's disease, uveal melanoma, Thyroid Related Immune Orbitopathy or clinically significant retinal pathology in either eye.

7. Subjects with any acute ocular disease that has not been completely treated and resolved for at least three months such as conjunctivitis, blepharitis, chalazion, corneal abrasion or keratitis in either eye.

8. Subjects with chronic systemic diseases which may affect the eye, including but not limited to diabetes, ulcerative colitis, systemic lupus erythematosus, Crohn's disease, collagen vascular disease, rheumatoid arthritis, any bleeding diathesis, or systemic manifestations of HIV/AIDS. Any other uncontrolled systemic disease (e.g., hypertension, cancer, etc.) that could compromise the patient's participation.

9. Use of any medication, such as coumadin, that could make the surgical procedure more difficult. Subjects using Coumadin, aspirin or NSAID medication under orders from a doctor must be able to provide written approval from the treating doctor for discontinuing this medication at least ten (10) days prior to surgery.

10. Subjects with chronic ocular surface disease, including but not limited to subjects with a prior diagnosis of chronic dry eye syndrome based on tests such as but not limited to, corneal or conjunctival staining, Ocular Surface Disease Index symptom score or Schirmer tear testing.

11. Subjects who are allergic to any medications used in the protocol.

12. Subjects who are pregnant, lactating, or of child-bearing age and not practicing a medically approved method of birth control

8.0 STUDY METHODS

8.1 Patient Screening and Enrollment

Prior to enrollment in the study, interested subjects will be screened to determine initial eligibility. The investigator or a designee will explain the study purpose and summary procedures and subject responsibilities to the potential subject. If it appears that the subject is interested and may be a candidate for the study, the subject will be asked to review and sign a Screening Informed Consent. The Screening Informed Consent provides a summary of the preliminary screening testing which will include standard of care testing including a medical history, vision testing and an examination of ocular health.

If preliminary eligibility is met, the subject will be asked to sign a Study Informed Consent Form which describes the surgical procedure; the potential benefits and risks, study examinations to be conducted, the frequency of follow-up visits, the expense reimbursement to be provided to the subject as well as other topics. When the Study Informed Consent is signed by the subject and by the Investigator or designee, the Subject is considered to be enrolled. Additional study specific testing of the subject's ocular and medical condition as specified in the baseline examination will be performed to determine eligibility. If during this testing, the Investigator or Sub-Investigator determines that the subject will not meet the protocol inclusion or exclusion criteria the examination may be terminated.

If the subject satisfies all inclusion and exclusion criteria, the full baseline examination data will be provided to the Sponsor for verification that all data have been obtained and meets eligibility criteria. Upon approval by the Sponsor, the subject will be scheduled for surgery if the subject has been enrolled and determined to be eligible at an Investigational site that is participating in the non-randomized cohort.

If the subject has been enrolled and determined to be eligible at an Investigational site that is participating in the randomized controlled sub-study, the subject will be randomized (1:1 ratio) to either the surgery group or the control group. Subjects randomized to the control group will be followed for 6 months, and will be eligible to undergo VisAbility Implant surgery after completion of the six month observation period.

8.2 Clinical Parameters and Examination Schedule

The clinical parameters to be recorded at baseline and post-operative examinations are shown in Table 1: Schedule of Visits and Measurements on the following page.

TABLE 1: SCHEDULE OF VISITS AND MEASUREMENTS

		Initial								Follow-up	
	Pre-Op	0 Day	1 Day	1 Week	1 Month	2 Months	3 Months	6 Months	12 Months	18 Months	24 Months
Slit Lamp Biomicroscopy OD, OS	✓[2]		✓	✓	✓	✓	✓	✓	✓	✓	✓
Applanation Tonometry OD, OS	✓[2]		✓	✓	✓	✓	✓	✓	✓	✓	✓
Gonioscopy OD, OS	✓								✓		
Scleral Thickness Measurement OD, OS	✓										
Implant Assessment OD, OS			✓	✓	✓	✓	✓	✓	✓	✓	✓
Axial Length / ACD OD, OS	✓								✓		✓
Corneal Topography / Keratometry OD, OS	✓										
Pupillometry OD, OS	✓[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Posterior Pole exam with 78 /90D lens OD, OS	✓[2]		✓		✓	✓	✓	✓		✓	
Dilated Indirect Ophthalmoscopy 20/30D lens OD, OS	✓			✓					✓		✓
Visual Fields OD, OS	✓										
Cup/Disk Ratio OD, OS	✓								✓		✓
Cycloplegic Refraction w/ VA OD, OS	✓								✓		✓
Manifest Refraction OD, OS	✓			✓[4]	✓	✓	✓	✓	✓	✓	✓
BCDVA OD, OS	✓[2]			✓	✓	✓	✓	✓	✓	✓	✓
UCDVA OD, OS	✓		✓[1]	✓	✓	✓	✓	✓	✓	✓	✓
UCNVA @ 40 cm OD, OS, OU	✓						✓	✓	✓	✓	✓
UCIVA @ 66 cm OU	✓						✓	✓	✓	✓	✓
DCNVA @ 40 cm OD, OS, OU	✓				✓	✓	✓	✓	✓	✓	✓
Patient Preferred Distance DCN - OD, OS, OU UCN - OU	✓						✓	✓	✓	✓	✓
Minimum add to achieve 20/20	✓						✓[3]	✓[3]	✓[3]	✓[3]	✓[3]
NAVQ (Validated PRO) & Patient Questionnaire	✓							✓	✓	✓	✓
Sub-Study Only Wavefront measurements[3]	✓						✓	✓	✓	✓	✓
Sub-Study Only Defocus Curve[3]	✓						✓	✓	✓	✓	✓

[1]Visual acuity will be measured using pinhole on day 1
[2]Fellow Eye Safety Exam (when fellow eye surgery is 61-180 days after primary eye surgery)
[3]Randomized Sub-study subjects only – control group subjects are examined through 6 months and the surgery group through 24 months.
[4]Measure BCDVA using baseline refraction

Examination methods are provided in Appendix 1: Examination Methods.

[redacted]

8.4 Post-Operative Care

Following surgery, physicians should adhere to the following guidelines of topical ophthalmic medications and care:

- To help control pain postoperatively, an icepack should be applied to the eye at intervals for approximately 30 minutes or longer as needed. A topical non-steroidal anti-inflammatory drug (NSAID) such as nepafenac ophthalmic suspension or equivalent may also be instilled immediately postoperatively. Chilled BSS may be instilled every 15 minutes and topical steroid drops such as prednisolone acetate 1% ophthalmic suspension or equivalent may be used every 15 to 30 minutes until the pupil reaction is greater than 25% as described in the next step. Prior to discharge the patient should be given Diamox 500mg Sequel PO or equivalent.

- Pupil functionality will be evaluated postoperatively using a NeurOptics Pupillometer every 15 to 30 minutes until the percent pupil constriction reading is at least 25%. A second, confirmatory reading may be taken as soon as 5 minutes after the first. If two pupil constriction readings of at 25% or greater are not achieved within the first 4 hours after surgery, preparation for removal of the implant segments will commence. The Investigator must remove all four implant segments no later than 6 hours after the surgery if two pupil constriction readings of 25% or greater are not achieved within 6 hours postoperatively.

- During the first week after the surgery, antibiotic drops such as moxifloxacin ophthalmic solution or equivalent and a topical steroid such as Lotemax gel or equivalent should be instilled in the eye. Additionally, NSAIDs such as topical nepafenac ophthalmic suspension or equivalent and / or oral medications such as naproxen or equivalent or acetaminophen with codeine or equivalent may be given as needed for pain during this time.

- Absorbable and / or non-absorbable conjunctival sutures may be removed at one week post-operatively or later as needed.

8.5 Scheduled Post-Operative Visit Schedule

8.5.1 Primary Eye Visit Schedule

Subjects enrolled and eligible in the non-randomized cohort of the study and subjects enrolled, eligible and assigned to the randomized surgery group will be examined according to the following schedule based on the date of primary eye surgery. Surgery on the primary eye may not occur more than 60 days after a baseline examination establishing eligibility. Visit windows are calculated on a 30 day month.

Pre-operative Baseline Evaluation	(Day -60 to Day -1)
Surgery	(Day 0)
One Day Exam	(18 to 36 hours)
One Week Exam	(7 days +/- 2 days)
One Month Exam	(1 month +/- 7 days)
Two Month Exam	(2 months +/- 14 days)
Three Month Exam	(3 months +/- 14 days)
Six Month Exam	(6 months +/- 21 days)
Twelve Month Exam	(12 months +/- 45 days)
Eighteen Month Exam	(18 months +/- 45 days)
Twenty-four Month Exam	(24 months +/- 60 days)

8.5.2 Subjects Randomized to the Control Group – Visit Schedule

Subjects enrolled, eligible and assigned to the randomized control group will be examined within the visit windows according to the following schedule.

Enrollment Randomization	(Day 0)
Three Month Exam	(3 months +/- 14 days)
Six Month Exam	(6 months +/- 21 days)

Subjects in the randomized control group that have completed the 6 month follow-up exam may elect to undergo placement of the VisAbility Implant. For these subjects, the 6 month visit will serve as the baseline eligibility examination. Subjects that undergo surgery will be examined in accordance with the primary eye visit schedule shown above.

8.5.3 Fellow Eye Visit Schedule

Subjects undergoing surgery in the fellow eye will be examined according to the following visit schedule. The one week and one month examinations may be combined with visits for the primary eye if the visit windows permit. After the one month visit, the fellow eye will be examined at the same time as scheduled follow-up visits for the primary eye.

Surgery	(Day 0)
One Day Exam	(18 to 36 hours)
One Week Exam	(7 days +/- 2 days)
One Month Exam	(1 month +/- 14 days)

If the fellow eye surgery is 61 to 180 days after the primary eye surgery, the fellow eye will be examined postoperatively after the one month visit, on a separate visit schedule for the 3 and 6 month visits only, established based on the same intervals and visit windows as shown above for the primary eye. Subsequent to the 6 month visit, the fellow eye will be examined at the same visit as the primary eye. Fellow eye and OU data will be recorded as attributable to the fellow eye visit timing through the fellow eye 6 month postoperative visit.

8.5.4 Fellow Eye Supplemental Baseline Examination

Fellow eye surgery may be performed 61 to 180 days after the baseline examination that has determined eligibility if a safety exam is performed and the findings do not alter the subject's continued eligibility. The following clinical parameters will be evaluated in the safety exam:

1. Medical history
2. BCDVA
2. Slit lamp biomicroscopy
3. Goldmann tonometry
4. Pupillometry
5. Posterior pole examination.

If fellow eye surgery is to be performed 181 days or more after a baseline exam determining eligibility, a complete baseline examination must be repeated. Baseline efficacy data for the fellow eye and for OU will always be from the baseline examination established prior to the primary eye surgical intervention.

8.5.5 Long-Term Follow-Up

Long-term follow-up (up to an additional 3 years beyond the end of this study) may be required by the FDA for this study. If required study participants will be examined according to the following schedule based on the primary eye surgery if they choose to participate,

Thirty-six Month Exam	(36 months +/- 60 days)
Forty-eight Month Exam	(48 months +/- 60 days)
Sixty Month Exam	(60 months +/- 60 days)

The clinical parameters to be recorded for these long-term follow-up examinations will be established in accordance with the FDA's requirements.

8.6 Data Collection

Sample paper source documents will be provided by the Sponsor for each subject enrolled and determined eligible in the study and will be completed by the Investigator or Sub-Investigator at the time of the subject examination. The source documents will be completed in a clear and legible manner in black or blue ink and then signed and dated by the Investigator as indicated on the form. Any correction will be made by drawing a single line through the incorrect entry, adding the correct entry, and then initialing and dating the corrected entry.

The information recorded on the source documents will then be entered into the electronic case report form (eCRF) in the Electronic Data Capture (EDC) System by the Investigator, Sub-Investigator or designee. The original dated and signed source document will be kept in the subject's study file at the Investigator's site. Instructions for the entry of data into the EDC will be provided to the clinical sites.

8.7 Study Completion

Subjects are considered to have completed the study when they complete the 24 month exam regardless of earlier missed visits. The length of participation of subjects in the study is as follows.

- Subjects enrolled and eligible in the non-randomized surgery cohort and subjects that are enrolled and eligible in the randomized surgery group as part of the randomized sub-study will participate in the study for 24 months.

- Subjects enrolled and eligible in the control group of the randomized sub-study who elect not to under surgery will participate in the study for 6 months.

- Subjects enrolled and eligible in the control group of the randomized sub-study who elect to undergo surgery after 6 months in the observation period will participate in the study for 30 months.

8.8 Subject Termination or Withdrawal

Subjects may be terminated from the study if the Investigator believes that continued participation in the study may jeopardize the subject's health or welfare. Subjects may also elect to withdraw from the study at their discretion. Every effort will be made to encourage the subject to maintain compliance with the protocol and to continue in the study. Further, every effort will be made in both instances to conduct examinations as determined by the Investigator to ensure the safety of the subject. The Sponsor should be notified promptly by the Investigator upon the termination or withdrawal of a subject by completion of the Study Exit form. Terminated or withdrawn subjects may not be replaced with additional enrolled and eligible subjects. Subjects who have all implant segments removed (explanted) from both eyes will be exited from the study after at least 3 months post-explant follow-up.

9.0 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.0 ADVERSE EVENT REPORTING

An Adverse Event ("AE") is any untoward sign, symptom or disease observed during the course of the study regardless of the suspected cause. Conditions or diseases that are pre-existing or chronic but stable are not Adverse Events. Changes in pre-existing or chronic conditions or diseases that are consistent with natural disease progression are not Adverse Events.

10.1 Serious Adverse Events (SAE)

An Adverse Event should be classified as a Serious Adverse Event ("SAE") and reported as such, if it meets one or more of the following criteria:

- It results in death (i.e., the Adverse Event actually causes or leads to death).
- It is life threatening (i.e., the Adverse Event places the subject at immediate risk of death).
- It is considered sight-threatening (i.e., the Adverse Event involves loss of vision at the time of diagnosis and carries a relatively grave prognosis of irrevocable loss of vision without timely high risk intervention).
- It requires or prolongs inpatient hospitalization (i.e., the Adverse Event requires at least a 24-hour inpatient hospitalization or prolonged hospitalization beyond the expected length of stay) Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions are not SAEs.
- It results in persistent or significant disability/incapacity (i.e., the Adverse Event results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It does not meet any of the above serious criteria but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

If a subject is hospitalized to undergo a medical or surgical procedure as a result of an Adverse Event, the event responsible for the procedure, not the procedure itself, should be recorded as the event. (For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass).

Investigators must notify Refocus of any SAE within 24 hours of observing or learning of the event. For initial SAE reports, Investigators should record all case details that can be gathered within 48 hours on the SAE Form and fax immediately upon completion to Refocus.

10.2 Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening or sight-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. UADEs also include any unanticipated sight-threatening events and any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Investigators must notify Refocus of any UADE within 24 hours of observing or learning of the event. Refocus will be responsible for informing Regulatory Authorities and all other IRBs and Investigators participating in the study of the UADE.

10.3 Adverse Event Assessment

All subjects who have been exposed to the study treatment will be evaluated for Adverse Events as defined in this protocol. All adverse events, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents using standard medical terminology. Pre-existing conditions or diseases present at baseline that remain stable or change in a manner consistent with natural disease progression are not considered Adverse Events.

All Adverse Events will be evaluated beginning at the time of onset, and evaluation will continue until resolution or until the investigator determines that the subject's condition is stable. The investigator will take appropriate and necessary therapeutic measures required for resolution of the Adverse Event. Any medication necessary for the treatment of an Adverse Event must be recorded on the concomitant medication source document.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Expectedness
- Relationship to study treatment
- Outcome
- Treatment or action taken.

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event.

If known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the source document rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). If a constellation of signs and/or symptoms cannot be characterized with a single medical diagnosis or syndrome and they are considered unrelated to an encountered syndrome or disease at the time of reporting, these individual events should be recorded as separate AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should each be recorded as an individual AE). If a diagnosis was not initially reported, and is subsequently established it should be reported as follow-up information and the original AE documents updated accordingly.

Adverse Events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

Orthostatic hypotension $\Rightarrow$ fainting and fall to floor $\Rightarrow$ head trauma $\Rightarrow$ neck pain

The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

10.4 Classification of Adverse Events by Intensity / Severity

All Adverse Events should be graded on a four-point scale (mild, moderate, marked, severe) for intensity/severity. These definitions are as follows:

Mild: Transient discomfort; no medical intervention/therapy required and does not interfere with daily activities.

Moderate: Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.

Marked: Considerable discomfort with limitation in daily activities, some assistance usually required; medical intervention/therapy usually required.

Severe: Extreme discomfort and limitation in daily activities, significant assistance required; ***significant*** medical intervention/therapy required.

There is a distinction between the severity and the seriousness of an Adverse Event. Severity is a measurement of intensity; thus a severe reaction is not necessarily a Serious Adverse Event. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for Serious Adverse Events.

10.5 Classification of Adverse Events by Expectedness / Relatedness

All AEs will be evaluated as to whether they are expected or unexpected, as defined below:

Expected (anticipated): An Adverse Event is expected when the nature, severity, or degree of incidence was previously described.

Unexpected (unanticipated): An Adverse Event is unexpected when the nature, severity, or degree of incidence was not previously described.

All AEs will be evaluated as to whether they are related to the device, as defined below:

Not Related: Strong evidence exists that the Adverse Event definitely has a cause other than the investigational device (e.g. pre-existing condition or underlying disease, concurrent illness, or concomitant medication), or the investigational device cannot be implicated based on the available information

Possibly Related: There is a temporal association with the investigational device and it cannot be excluded as a cause but other etiologies are also likely to be the cause based upon available information

Probably Related: There is a temporal association with the investigational device which makes a causal relationship probable where other etiologies are possible but unlikely to be the cause, based upon available information.

Definitely Related: Strong evidence exists that the investigational device definitely caused the Adverse Event. There is a temporal relationship between the event onset and the investigational device and the subject's clinical state and concomitant therapies have

been ruled out as a cause, based upon available information.

10.6 Adverse Event Outcome

The clinical outcome of an Adverse Event will be recorded and characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death.

10.7 Treatment or Action Taken

The clinical treatment of an Adverse Event will be documented and characterized as follows:

- None
- Medical Intervention
- Surgical Intervention
- Other

10.8 Anticipated Adverse Events

Adverse Events that might reasonably be expected to occur in this study are listed below. The time periods refer to the exam visit that occurs corresponding to the post-operative follow-up visit schedule (i.e., 3 months means the 3 month postoperative visit). Exams for the primary eye and fellow eye may be done at the same visit if windows permit. For purpose of determining whether a fellow eye event is an Adverse Event, the time period used shall be based on the date of the fellow eye surgery.

These specific examples of anticipated Adverse Events include, but are not limited to:

Intraoperative Events

- Scleral perforation
- Scleral perforation with vitreous prolapse

Lids and Lashes

- Ptosis
- Onset of or worsening to severe clinically significant lid margin disease (e.g., blepharoconjunctivitis, blepharitis, meibomitis, meibomian gland dysfunction, etc.) after 3 months postoperative

Cornea

- Corneal dellen after 1 week postoperative
- Corneal abrasion > 2mm after 1 week postoperative
- Dry eye signs (moderate or severe) of corneal and/or conjunctival staining, etc., requiring prescription medication after 6 months postoperative
- Corneal edema (moderate or severe) after 1 month postoperative
- Corneal infiltrate or ulcer

Conjunctiva/Sclera

- Conjunctival cyst
- Conjunctival thinning or erosion
- Moderate or severe conjunctival injection at 3 months postoperative or later
- Subconjunctival hemorrhage after 3 months postoperative

Anterior Segment, Iris, Lens

- Pupil abnormalities persisting after 3 months
- Grade 4 anterior segment ischemia (corneal edema, anterior chamber reaction, and decreased pupil reactivity)*
- Anterior chamber cells or flare greater than mild at Day 1 through 1 Week
- Anterior chamber cells or flare after 1 week postoperative
- Intraocular Inflammation other than anterior chamber cells and flare (e.g.,vitritis)
- Two grade change in lens opacity compared to baseline on two consecutive post-operative visits
- Displaced or missing implant segments

Intraocular Pressure

- Hypotony (IOP < 6mmHg)
- Increase in IOP of > 10mm Hg over baseline or IOP > 30mm Hg at two consecutive visits at 1 week or later

BCDVA Loss

- Decrease in BCDVA of greater than or equal to 2 lines (≥10 letters ETDRS) at 3 months or later

Fundus

- Choroidal effusion
- Retinal detachment
- Retinal or vitreous hemorrhage

Secondary Surgical Intervention

- Implant segment removal
- Exposed implant segments or conjunctival retraction requiring conjunctival re-approximation

Other

- Eye pain requiring oral prescription pain medication after 1 week postoperative
- Allergic reactions to medications, devices, sutures or anesthesia
- Other findings worsening two grades from baseline to a grade of +3 or +4

* Refer to Appendix 6: Anterior Segment Ischemia (ASI): Detection, Mitigation and Reporting

11.0 STATISTICAL METHODS

This is a prospective, multicenter study with a randomized, controlled sub-study that is designed to evaluate the safety and effectiveness of the scleral implant procedure. The percentage of primary eyes achieving the effectiveness endpoint will be evaluated at 12 months postoperatively. Within the study cohort, a subgroup will be randomized on a 1:1 ratio to a surgery group and a control group. Subjects in the randomized control group will not receive surgery and will be examined at 3 months and 6 months. After completion of the 6 month observation period, subjects in the randomized control group will be eligible to receive surgery as part of the 360 subject cohort. This randomized controlled sub-study will be used to evaluate the effectiveness of the scleral implant procedure in the randomized surgery group compared to effectiveness in the randomized control group at 6 months postoperatively.

The effectiveness endpoint, hypotheses, sample size calculations, analysis population, handling of missing data, analysis methods, and analysis of safety data are as follows.

11.1 Effectiveness Endpoint

The effectiveness endpoint is:

> Achievement of distance corrected near visual acuity (DCNVA) of Snellen equivalent 20/40 or better (at 40 cm) and at least 10 letters (ETDRS) improvement in DCNVA in the primary eye.

11.2 Statistical Hypotheses

For the effectiveness endpoint, two objectives must be met.

> Objective #1:
> The scleral implant procedure is defined as successful if 75% or more of primary eyes achieve the effectiveness endpoint at 12 months postoperative. The corresponding statistical hypothesis is as follows:
>
> H_0 (null hypothesis): $p < 0.75$
>
> H_a (alternative hypothesis): $p \geq 0.75$
>
> Where, p is the probability that subjects achieve the effectiveness endpoint at 12 months postoperative (12-month responder rate).
>
> Objective #2:
> An analysis of the randomized surgery group and randomized control group will be conducted. The randomized surgery group is defined as successful if the percentage of primary eyes achieving the effectiveness endpoint at 6 months postoperative (6-month responder rate) is higher than the percentage in the randomized control group. The corresponding null and alternative hypotheses are as follows:
>
> H_0 (null hypothesis): $p_1 \leq p_2$
>
> H_a (alternative hypothesis): $p_1 > p_2$
>
> Where:

- p_1 is the percentage of primary eyes in the randomized surgery group who achieve the effectiveness endpoint at 6 months.
- p_2 is the percentage of primary eyes in the randomized control group who achieve the effectiveness endpoint at 6 months.

The primary eye is defined as the subject's dominant eye and the eye that will undergo surgery first. It is intended that all subjects will also undergo surgery in the fellow eye at a subsequent date as specified in the protocol.

11.3 Sample Sizes

Both Objective #1 and #2 will need to be statistically significant in order to determine the effectiveness of the study device. Therefore the two-sided significance level of 0.05 is not adjusted for the multiplicity.

Full Study Cohort Effectiveness Endpoint

The sample size calculation for the statistical hypotheses described for Objective #1 in Section 11.2 is based on the following criteria:

- The two-sided significance level = 0.05 (or one-sided significance level = 0.025).
- The statistical power = 90% at p = 0.825. The assumption of true responder rate of 0.825 is based on the simple average of success rate observed in previous Refocus clinical study data, as follows:
  - Disposable Scleratome group had an observed success rate of 88%.
  - Re-usable Scleratome group had an observed success rate of 77%.
  - Simple average of 88% and 77% is 82.5%.
- Binomial distribution is used for sample size calculation.

Based on the criteria above for Objective #1, 330 treated primary eyes should be available for analysis at 12 months. If a dropout rate of 10% of subjects by 12 months is considered, then the surgery cohort should include approximately 360 treated primary eyes.

For safety analysis, in order to detect an Adverse Event (AE) with a true probability of occurrence among subjects of 1% with 95% probability, based on the binomial distribution, a sample of at least 299 eyes would be required (in accordance with ANSI Z80 29 18Nov2013 AIOL [rev20]). Assuming a drop-out rate of approximately 10% of subjects by 12 months, the surgery cohort should include a minimum of 333 treated primary eyes.

A sample size of 333 treated primary eyes will meet the sample size requirements for both safety and effectiveness. The study cohort is planned for 360 surgery subjects at up to 14 study sites. However, no site may enroll and determine to be eligible more than 20% of the subject surgery cohort.

Randomized Sub-study

The sample size for Objective #2 in Section 11.2 is based on the following criteria:

- The two-sided significance level = 0.05 (or one-sided significance level = 0.025).

- Based on the randomized control group data collected in IDE G970152, the 6-month responder rate is estimated as 10% for the control group.
- Based on the surgery group data collected in IDE G970152, the 6-month responder rate was lower than the 12-month responder rate. Therefore, it is assumed that the 6-month responder rate of the randomized surgery group in this study will be approximately 0.75.
- The statistical power = 90%.
- Fisher's exact test is used for sample size calculation.

Based on the criteria above, a sample of 14 randomized surgery group primary eyes and 14 randomized control group primary eyes at 6 months will ensure a power greater than 90% for Objective #2, using a one-sided alpha of 0.025.

A sample size of 30 randomized surgery group subjects and 30 randomized control group subjects has been selected which will account for a possible 10% subject drop-out rate and allow for greater accuracy in point estimates for both groups. This randomized sub-study will be conducted at 3 clinical sites. Sites will be chosen based on availability of equipment for additional sub-study measures, such as availability of an iTrace unit (Tracey Technologies, Houston, TX), and the ability and willingness of the site to participate in the additional sub-study. The target enrollment at each of the 3 sites in the randomized sub-study will be 20 eligible subjects to provide an even distribution. However, no site may enroll and determine eligible more than half of the randomized sub-study cohort or 30 subjects.

11.4 Cohort Population

Potential subjects will sign a screening consent to undergo preliminary screening for eligibility that consists of standard of care eye examinations. Subjects who may be eligible based on the preliminary screening criteria and are willing to participate in the study will sign a full informed consent and are considered enrolled. At that time, the study specific examinations required to complete the baseline examination will be administered to determine eligibility for the study. Subjects who have signed the full informed consent but do not meet all of the inclusion and exclusion criteria will be considered enrolled but ineligible for the study. The reason for the disqualification will be recorded and reported.

Safety Cohort: All eyes (both primary and fellow eyes) that have undergone surgical preparation of the ocular surface.

Effectiveness Cohort: All primary eyes that have been implanted with at least one implant segment and primary eyes of subjects that have been enrolled and determined eligible in the randomized control group.

Figure **9**, below, summarizes the status of enrolled subjects and the cohort populations for the study, except that the randomized control group is not shown.

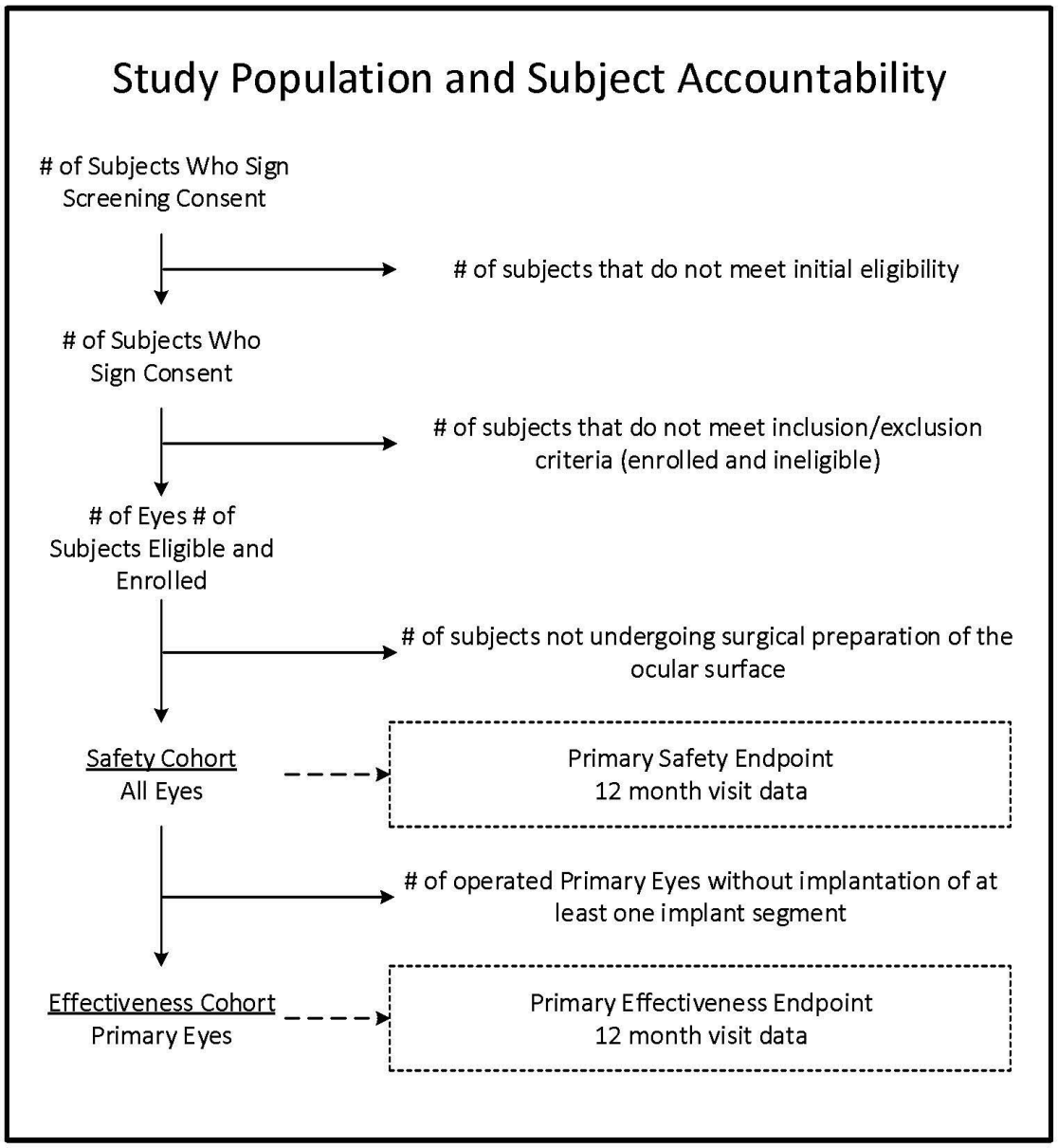

FIGURE 9 – ILLUSTRATION OF STUDY POPULATION AND ACCOUNTABILITY

11.5 Subject Accountability

The following terms and definitions will be used for the accountability of the study population and are based on the definitions found in ANSI Z80.29 Rev 018, section B.5.3 as modified and explained below.

- Enrolled – the total number of subjects that have signed the full informed consent.
    - Enrolled but ineligible – the total number of subjects that have signed the full informed consent but do NOT meet all of the inclusion/exclusion criteria.
    - Enrolled and eligible – the total number of subjects that have signed the full informed consent and meet all of the inclusion/exclusion criteria.
- Surgical Withdrawal – Subjects (eyes) that have been enrolled and determined eligible but do not undergo surgical preparation of the ocular surface for any reason.
- Discontinued– Subjects (eyes) that have discontinued treatment prior to the visit window associated with the form as a result of death, the removal of all 4 implant segments (explant), or any other reason except lost to follow-up.
    - Explanted Eye – Eyes that underwent implantation surgery, but have had all implanted segments removed.
- Lost to Follow-up – Subjects that have withdrawn from the study after initial eye surgery or subjects that have missed the visit window associated with the form and all subsequent scheduled visits despite documented efforts by the Investigator to schedule the subject for follow-up.
- Missed Visit – Data for subjects (primary eyes) that is not available for a follow-up visit within the specified visit window associated with the form, but data is available for a subsequent follow-up visit for such subject.

11.6 Analysis of Effectiveness Cohorts

For the primary analysis of Objective #1, all observed 12-month data of the surgical primary eyes will be included in the effectiveness analysis. Missing data will not be imputed except that explanted primary eyes will be imputed as failures.

For the primary analysis of Objective #2, all reported 6-month data of the randomized primary eyes will be included in the analysis. Missing data will be imputed as follows:

- Randomized Control Group: In the absence of 6 month visit data, the nearest available data recorded between and including the 3 month visit up to the 6 month visit will be utilized. Since this randomized control group does not receive the benefit of the surgery during this 6 month observation period, the lost to follow-up and missed visit rate could be higher and since no intervention occurs during the 6 month period, this imputation of missing data is warranted. In the absence of any observed data between the 3 month visit

and 6 month visit, this missing data will not be imputed since failure to achieve the effectiveness endpoint is expected.

- Randomized Surgery Group:
    - Explanted primary eyes will be imputed as failures.
    - In the absence of 6 month visit data, the nearest recorded data after 6 months up to and including 12-month visit data will be used. This imputation is warranted as the visit data between 6 and 12 months provides a predictive indicator of 6 month results. In the absence of any observed data between 6 and including 12 months, this other missing data will not be imputed.

11.7 Baseline Demographic Characteristics

Demographic data including, but not limited to, age, race, sex and ethnicity and baseline characteristics including, but not limited to, DCNVA, UCNVA, UCDVA, BCDVA, manifest refraction spherical equivalent (MRSE), cycloplegic refraction spherical equivalent (CRSE), will be reported for each subject. Baseline characteristics such as age, sex, race, and near visual acuity will be summarized.

11.8 Analysis of Effectiveness Data

As noted previously, both Objective #1 and Objective #2 of the primary effectiveness endpoint must be satisfied in order for the study to be considered a success.

Analysis of Objective #1:

The one-sided 97.5% lower confidence limit of the 12-month responder rate will be calculated based on the exact binomial distribution. This goal is met if the one-sided 97.5% lower confidence limit of the 12-month responder rate is at least 75%.

The percentage of primary eyes achieving the Effectiveness Endpoint at 12 months will be compared among the study sites. The Fisher's exact test will be used to evaluate the possible study site effect. If the site effect is significant, i.e., p-value ≤ 0.15, then 12-month responder rates stratified by study site will be provided and the average of the site 12-month responder rates will be calculated. The normal distribution approximation will be used to estimate the one-sided lower 97.5% confidence limit for the average 12-month responder rate.

Fisher's exact test will also be used to assess the effects of subject sex, race and age category at surgery on the 12-month responder rates for primary eyes using a p-value of 0.15. For this analysis, age will be categorized into 3 interval groups (i.e., 45-49, 50-54, and 55-60).

Analysis of Objective #2:

The number and percentage of primary eyes achieving the Effectiveness Endpoint at 6 months will be summarized for the randomized surgery group and randomized control group separately. The two-sided Fisher's exact test will be used to compare the difference between 6-month responder rates of the two randomized groups.

In order to assess potential differences of randomized group allocation and/or site 6-month responder rates, a logistic regression analysis examining with the following will be performed:

- treatment effect (the randomized surgery group and the randomized control group at that same site),
- study site effect (site by site success rate comparison), and
- site by treatment interaction

If there is a significant difference ($p \leq 0.15$) in treatment effect, study site effect, or a significant interaction effect between study site effect and treatment effect ($p \leq 0.15$), then the 6-month responder rate for each study group and the difference in the 6-month responder rate between the two randomized groups ($p_{treatment} - p_{deferred}$) will be summarized by each study site.

Sensitivity Analysis of Objective #1:

Sensitivity analysis will be performed for Objective #1 using the following imputation methods for missing 12-month data:

- Best Case Analysis: All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes lost to follow-up or for primary eyes missing 12-month visit data, the best value from any protocol scheduled visit at 1 month or later (1 month, 3 month or 6 month visit) will be used. If such visit data does not exist for a primary eye, the effectiveness will be imputed as a success.

- Worst Case Analysis: All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes lost to follow-up or missing 12 month visit data, the worst value from any protocol scheduled visit at 1 month or later (1 month, 3 month or 6 month visit) will be used. If such visit data does not exist for a primary eye, the effectiveness will be imputed as a failure.

- Tipping Point Analysis: All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes missing 12-month visit data for reasons other than discontinued, effectiveness will be initially be set to success. At this step, the lower limit of the one-sided 97.5% confidence intervals (CI) will be calculated. Serial calculations will then be performed using a decreasing number (i.e., n-1, n-2, …1) of successes to determine the maximum number of additional failures allowed for the lower bound one-sided 97.5% CI of the effectiveness endpoint percent estimate to achieve or exceed 75% success.

Sensitivity Analysis of Objective #2:

- Tipping Point Analysis: All discontinued primary eyes will be iteratively imputed as effectiveness success or failures. Let n_1 and n_2 be the number of discontinued primary eyes for the randomized surgery group and the randomized control group, respectively. For the n_1 discontinued randomized surgery group primary eyes, they can be imputed as 0 failures, 1 failure, 2 failures, and up to n_1 failures, for a total of (n_1+1) possible imputations. For the n_2 discontinued randomized control group primary eyes, there are (n_2+1) possible imputations. Therefore, there are $(n_1+1) \times (n_2+1)$ possible combinations of success and failure imputations for these discontinued

primary eyes. For each of these possible imputations, the lower limit of the one-sided 97.5% confidence intervals (CI) will be calculated. The imputations that have the lower one-sided 97.5% CI < 75% will be identified.

11.9 Analysis of Safety Data

Safety data such as BCDVA, slit lamp findings, and fundus findings will be summarized descriptively (mean, standard deviation, minimum, and maximum for continuous outcomes, and counts and percentages for categorical outcomes) for primary and all eyes.

For IOP at each visit, the mean, standard deviation, minimum and maximum and change from baseline will be summarized for all implanted eyes. Additionally, number and percentage of eyes with a IOP change from baseline of "decrease > 10 mmHg", "decrease ³ 5 mmHg to ≤ 10 mmHg", "change within ± 4 mmHg", "increase³ 5 mmHg to ≤ 10 mmHg", and "increase > 10 mmHg" will be prepared for each study visits.

Manifest spherical equivalence (MRSE) will be summarized descriptively with the 95% confidence interval for the mean for primary eyes and all eyes at each visit. Additionally, the same analyses will be performed on the MRSE adjusted by normal aging (i.e., minus 0.082 D per year[1,2,3,4]).

11.10 Analysis of Other Clinical Parameters

Means, standard deviations, and ranges will be derived from the continuous measurements; numbers and percentages will be used for summarizing the categorical outcomes. No specific claims will be made based on outcomes not pre-specified as an endpoint and no p-values will be presented for analyses without a pre-specified hypothesis.

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[5] Buckhurst, P.J., et al., *Development of a questionnaire to assess the relative subjective benefits of presbyopia correction.* J Cataract Refract Surg, 2012. **38**(1): p. 74-9

12.0 STUDY MONITORING

Sponsor or CRO personnel will monitor all clinical studies in accordance with FDA guidelines. Study monitoring will involve the following elements:

- Sponsor or CRO personnel will meet with Investigators prior to the initiation of the study in order to review the adequacy of the facility, equipment and clinical personnel with respect to the needs of the study and to familiarize the Investigator and clinic staff with the protocol.

- Sponsor or CRO personnel will meet with Investigators and clinic staff at initiation of the time of study to ensure that subjects are being properly consented, the protocol examination methods are being complied with and that study data is being properly recorded.

- Sponsor or CRO personnel will meet with the Investigator and clinic staff at any time during the study regarding study conduct to ensure ongoing compliance with the protocol and data recording requirements.

- Sponsor or CRO personnel will maintain ongoing email and telephone communication with the Investigator and clinic staff regarding study conduct.

- The CRO shall select, train and manage qualified contract personnel to visit each Investigational site to review and monitor source documents and electronic data in accordance with FDA guidance.

13.0 REFERENCES

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APPENDIX 1: EXAMINATION METHODS

Refractions and acuity measurements shall be obtained by an ophthalmologist, optometrist or trained technician (who is supervised directly by the ophthalmologist or optometrist).

Manifest Refraction

Manifest refraction will be performed pre and post-operatively using ETDRS acuity charts and standard phoropters. All systems will employ actual or equivalent optical distances of at least 4 meters (13 feet) and ambient lighting will be adjusted based on chart specifications. Chart luminance will fall within the ANSI required range of 80-160cd/m2 and chart contrast will be a minimum of 85%.

Cycloplegic Refraction

Cycloplegic refraction will be performed ~ 20 minutes after application of 1 drop of tropicamide 1% at select pre and post-operative visits using the same systems as for manifest refraction.

Instrument for Measuring Visual Acuities

All visual acuities will be measured via the OPTEC 6500 (Stereo Optical, 8623 W. Bryn Mawr Ave., Suite 502, Chicago, IL 60631 USA 1.773.867.0380 or 1.800.344.9500). This system utilizes a lens system to simulate various test distances for distance, intermediate and near. The Optec 6500 has a microprocessor controlled internal illumination system that results in constant luminance of 85cd/m^2; therefore, normal ambient lighting may be used as lighting conditions are not a factor in the testing set up. The manufacturer's instructions for use will be provided to each Investigational site.

Distance Visual Acuity

Distance visual acuity will be measured at a simulated (optical) distance of 20 feet.

Intermediate Visual Acuity

Intermediate visual acuity will be measured at a simulated (optical) distance of 66cm.

Near Visual Acuity

Near visual acuity will be measured at a simulated (ocular) distance of 40cm.

Determination of Near Add

The add power will be determined by adding plus lenses, using the Optec 6500 at a simulated distance of 40cm.

Determination of Dominant Eye

The subject will be advised to perform the following steps for determination of the dominant eye.

1. Hold your hands at arm's length out in front of you. Your palms should be pointing forward - in other words, you should be looking at the backs of your hands.
2. Make a "triangle." Extend both of your thumbs so that they're roughly perpendicular to the rest of the hand. Overlap your hands so that the space between makes a triangle. Your two

thumbs should be at the bottom of the triangle, while the edge and index finger of each hand form the two remaining sides.

3. The triangle space between your hands acts as a viewing window - you should be able to clearly see objects through it.

4. Look at an object through the triangle hole made by your hands with both eyes open. Find a nearby object that's small enough (or far enough away) that you can see the whole object through the viewing window between your hands. This can be anything - a door knob, a coffee mug, or even a letter on a faraway billboard.

5. Focus on the object. Try to focus your eyes on the object between your hands - not your hands themselves. Your hands should become somewhat blurry, while the object remains clear and in-focus. It's important to line this object up directly in front of you and to stare straight at it - turning your head to either side can distort your results.

6. For best results, at this point, make minor adjustments to your hands so that the object you're looking at fits almost exactly within the edges your viewing window. In other words, if your triangle is bigger than the object you're looking at, move your hands together to make it smaller, and vice versa.

7. Alternate closing each eye to see which gives better vision. Close one eye, then open it and close the other. Each time you switch eyes, the object you're looking at should do one of two things. It should either become obscured behind one of your hands *or* remain visible. Next, try your other eye. Your dominant eye is the one that allows you to see the object while it remains open.

Scleral Thickness Measurement

Scleral thickness will be measured and printed using the Sonomed Ultrasonic Biomicroscope (UBM). The manufacturer's instructions for use will be provided to each Investigational site.

Pupil size, shape and reaction

The NeurOptics Pupillometer is a portable, battery-operated, hand-held device used to measure the iris' reaction to a standardized level and duration of light. The manufacturer's instructions for use will be provided to each Investigational site.

The pupils of both eyes will be assessed at each and every visit as follows:

- Round
- Elliptical
- Irregular

Slit Lamp Evaluation – Grading

Lids / Lashes

Blepharitis (using the Efron Grading scale and reference drawings):

- 0 = none
- 1 = trace (1+)
- 2 = mild (2+)
- 3 = moderate (3+)
- 4 = marked / severe (4)

Meibomian Gland Dysfunction (using the Efron Grading scale and reference drawings):

- 0 = none
- 1 = trace (1+)
- 2 = mild (2+)
- 3 = moderate (3+)
- 4 = marked / severe (4)

Cornea

Superficial punctate keratitis (using the Efron Grading scale and reference drawings):

- None
- Mild
- Moderate
- Marked or Severe

Corneal abrasion:

- None
- Tiny
- 1-2mm
- 2-3mm
- > 3mm

Corneal edema (using the Efron Grading scale and reference drawings):

- 0 = no evidence of corneal edema
- 1 = trace corneal edema (edema involves 0% to 5% of the cornea)
- 2 = mild corneal edema (edema involves 5% to 25% of the cornea)
- 3 = moderate corneal edema (edema involves 26% to 50% of the cornea)
- 4 = marked/severe corneal edema (edema involves > 50% of the cornea)

Corneal endothelial gutatta:

- 0 = no corneal gutatta
- 1 = rare corneal gutatta
- 2 = few corneal gutatta
- 3 = many corneal gutatta
- 4 = marked/severe corneal gutatta with stromal edema and bullous lesions
- Other abnormal corneal findings (specify)

Conjunctiva

Conjunctiva injection (using the Efron Grading scale and reference drawings):

- 0 = none
- 1 = trace (1+)
- 2 = mild (2+)
- 3 = moderate (3+)
- 4 = marked/severe (4)

Subconjunctival hemorrhage:

- 0 = none
- 1 = less than or equal to 1 quadrant
- 2 = 2 quadrants
- 3 = 3-4 quadrants

Conjunctiva edema:

- 0 = none
- 1 = trace
- 2 = mild
- 3 = moderate
- 4 = marked/severe

Other abnormal conjunctival findings (specify)

Crystalline Lens

Crystalline lens pathology using the LOCSII scale (with reference photos as published in Archives of Ophthalmology July 1989) as follows:

- Normal
- Lens Opacity
- Other Abnormal Findings (specify)

If lens opacity, please complete the following:

- Nuclear/Color Opalescence: □ N0 □ N1 □ N2 □ N3
- Cortical: □ C0 □ C1 □ C2 □ C3 □ C4
- Posterior Subcapsular: □ P0 □ P1 □ P2 □ P3
- Anterior Subcapsular: □ A0 □ A1 □ A2 □ A3

Anterior Chamber

Cell and flare will be graded according to the SUN grading scheme (using a 1x1 mm slit lamp beam):

SUN Grading for AC Cells

GRADE	CELLS IN 1x1mm Field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	50+

SUN Grading for AC Flare

GRADE	Description
0	None
1+	Faint
2+	Moderate (iris/lens details clear)
3+	Marked (iris/lens details hazy)
4+	Intense (fibrin/plastic aqueous)

Iris appearance

- 1 = Normal
- 2 = Abnormal (if abnormal, please describe)

Intraocular Pressure

Intraocular pressure will be measured using Goldmann applanation tonometry. Measurements will be taken according to the published guidelines set forth by Michael A. Kass [*Kass MA. Standardizing the measurement of intraocular pressure for clinical research. Guidelines from the Eye Care Technology Forum. Ophthalmology. 1996 Jan;103 (1):183-5*]. Copies of this guideline will be provided to all sites.

Gonioscopy

The angle will be evaluated using a 3 or 4 mirror lens and the following grading scheme:

- Grade 3 – 4 (Wide Open: Angle > 20 degrees < 45 degrees)
- Grade 2 (Moderately Narrow: Angle = 20 degrees)
- Grade 1 (Extremely narrow: Angle = 10 degrees)
- Grade 0 (Angles Closure: Angle + 0 degrees
- Other: (Specify)

A-Scan

Axial length and ACD will be measured and recorded.

Internal Examination

Peripheral Fundus Examination

- Normal
- Abnormal (if abnormal, please describe)

Cup to Disc Ratio will be assessed by means of a dilated fundus exam using condensing lenses and the slit lamp biomicroscope.

Other Observations:

Photographs, drawings and / or standard descriptive ophthalmic terms may be used as needed to describe any other ocular findings.

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APPENDIX 5: DATA SAFETY MONITORING BOARD CHARTER

Refocus Group, Inc.

DATA SAFETY MONITORING BOARD (DSMB) CHARTER

A PROSPECTIVE, MULTICENTER CLINICAL TRIAL OF

THE VISABIITY IMPLANT SYSTEM (VIS)

FOR THE IMPROVEMENT OF NEAR VISUAL ACUITY IN PRESBYOPIC PATIENTS

Protocol: VSI-2014

Date of Protocol: October 13, 2014
Date of Protocol Amendment 1: January 10, 2015

1. INTRODUCTION

This charter governs the Data Safety Monitoring Board (the "DSMB") established by Refocus Group, Inc. (the "Sponsor") for the prospective, multicenter clinical trial of the VisAbility Implant System for the improvement of near visual acuity in Presbyopic patients under Protocol VIS-2014 (the "Clinical Trial"). The charter describes; the role and responsibilities of the DSMB, its members, conduct of meetings, its access to data and the manner of communication with the Sponsor.

2. ROLE OF THE DSMB: RESPONSIBILITIES & FUNCTION

The primary role of the DSMB will be to ensure subject safety during the conduct of the Clinical Trial.

The DSMB will periodically evaluate the conduct of the Clinical Trial, adverse events and related safety data, and efficacy data from the perspective of relative benefit. The DSMB will make recommendations to the Sponsor as follows.

The recommendations of the DSMB to the Sponsor may include:

Modification of the study protocol, subject to approval of FDA or the IRB as applicable.

Continuation of the study according to the protocol and any related amendments.

Modification of the manner of study conduct.

Discontinuation of the study (with provisions for orderly discontinuation in accord with good medical practice).

Discontinuation of enrollment into the study.

3. DSMB MEMBERSHIP

3.1 Members

The DSMB will consist of three members with at least two members being licensed ophthalmologists or optometrists. The names and contact information of the DSMB members are as shown in the Appendix and will be updated periodically as needed should changes in DSMB membership occur. A copy of each DSMB member's curriculum vitae, updated at least annually, will be maintained by the Sponsor and available upon request. DSMB members will not act as investigators or sub-investigators for the Clinical Trial and will have no involvement in the Clinical Trial outside their role on the DSMB. DSMB members may not participate in any other IDE clinical study of a presbyopia correcting surgical device or technique, other than studies of presbyopia correcting intraocular lenses, nor may DSMB members serve as a personal physician to any subject enrolled in the Clinical Trial.

3.2 Financial Disclosure and Conflict of Interest

Each DSMB member must disclose any financial or other material interests which may create a potential conflict with respect to their role on the DSMB including, but not limited to, equity interests in the Sponsor. Members of the DSMB will be responsible for advising the Sponsor of any change in related financial interests.

The Sponsor will be responsible for deciding whether financial or material interests may impact a member's objectivity, and may ask a member to resign from the DSMB.

3.3 Duration of DSMB Membership and Replacement of Members

The DSMB membership will cover the duration of the Clinical Trial, including any extension of the follow-up period of the subjects.

3.4 Replacement of Members

If a member cannot continue to serve on the DSMB, the reason must be communicated in writing to the DSMB Chairperson and the Sponsor. If a member or the Chairperson leaves the DSMB, the Sponsor will select an appropriate replacement. If a member cannot reasonably be available for meetings of the DSMB, the Chairperson may request the member be replaced and the Sponsor may remove such member with the recommendation of the Chairperson. The Sponsor will be responsible for providing any new DSMB member with necessary study related materials.

4 DSMB MEETINGS

The DSMB will meet in person or by conference call according to the following schedule.

4.1 Initial Organizational Meeting

The initial meeting of the DSMB will be to acquaint the DSMB members with Protocol VIS-2014, Sponsor personnel, Sponsor communication, planned study conduct as well as other pertinent information. The DSMB may also recommend changes to this charter during this organizational meeting. Invited attendees include the DSMB members, the Medical Monitor and the Sponsor’s representatives.

4.2 Scheduled Meetings

Meetings will be held by phone or in person twice per year during the Clinical Trial. The frequency of scheduled meetings may change at the discretion of the DSMB Chairperson depending on subject enrollment and safety event rates. Meetings will also be held upon the occurrence of a device-related SAE or UADE, or at the request of the Medical Monitor.

4.3 Quorum and Voting

A quorum of two of the three DSMB members is required to hold any teleconference or in-person meeting. All three DSMB members must participate for a vote on any recommendation to the Sponsor other than normal continuance of the Clinical Trial.

4.4 Meeting Format

The meeting will begin with an open session to review enrollment, study conduct and safety information generated in the Clinical Trial. Representatives from the Sponsor and the Medical Monitor will present the information and answer any questions from the DSMB.

A closed session will follow to discuss safety data and any actions required by the DSMB regarding the available safety information. This session will be attended by only the DSMB members and, if requested with reasonable advance notice, an independent statistician retained by the Sponsor with access to the Clinical Trial database. The DSMB members will discuss the safety data, formulate any recommendations, and conduct their voting.

A final session will then convene to be attended by the DSMB members and representatives from the Sponsor and the Medical Monitor. The DSMB will verbally convey its recommendations to the Sponsor's representatives. The DSMB Chairperson will convey written DSMB recommendations within a timely fashion (within three weeks after the meeting) to the Sponsor.

5 COMMUNICATION

5.1 Data Reports

The Sponsor will prepare and provide safety data to the DSMB in advance of each meeting. All available data will be used to create a summary report and summary tables of safety data, listings of adverse events and specific case histories for selected AEs, SAEs or UADEs. The data in these tables will be drawn from active study databases. The Sponsor and Medical Monitor shall present and explain the data in the open session to the DSMB and answer any questions. The DSMB Chairperson may, on behalf of the DSMB, communicate in advance to the Sponsor a request for additional information and the Sponsor shall make reasonable efforts to comply.

If requested, the Sponsor will designate an independent statistician with access to the Clinical Trial database to be available to prepare and provide data directly to the DSMB regarding the Clinical Trial effectiveness outcomes.

The DSMB chairperson will be notified by the Sponsor or Medical Monitor upon the occurrence of a device-related SAE or UADE.

If the DSMB requests additional information concerning the study data, the DSMB Chairperson may contact the Sponsor’s designated independent statisticians directly and the statistician shall be instructed by the Sponsor to provide any information reasonably requested.

5.2 DSMB Minutes

Following each meeting, summary minutes of both the open and closed meeting sessions will be drafted and distributed on a timely basis for approval. Minutes from open session meetings will be compiled by a Sponsor representative and reviewed by Sponsor representative(s) as well as DSMB members attending the meeting. Minutes from closed session meetings will be compiled by a DSMB member and reviewed only by DSMB members attending the meeting. Both open and closed session meeting minutes will be retained throughout the study by the DSMB Chairperson. The minutes of both open and closed meetings will be approved by the DSMB at the subsequent meeting.

Upon completion of the Clinical Trial follow-up period and the locking of the database by the CRO, the DSMB will forward a complete set of both open and the closed meeting minutes to the Sponsor.

5.3 DSMB Recommendations

At each DSMB meeting, the DSMB will recommend whether the study should continue, stop, or be modified based on study findings. The DSMB will provide written recommendations about the trial to the Sponsor within a timely fashion but not longer than three weeks after the meeting. In addition, the DSMB will also communicate verbally with the Sponsor's representatives immediately regarding any safety issues or other findings.

Upon receipt of the DSMB recommendations, the Sponsor will consider the recommendations, review the status of the Clinical Trial, and determine a timely course of action.

The Sponsor may identify expert individuals to review the DSMB Reports. These individuals will not have any direct involvement with the Clinical Trial but will have the clinical, statistical, and regulatory expertise needed to contribute to any decisions on behalf of the Sponsor. The Sponsor may seek input from regulatory agencies and make a decision to accept or disregard the recommendation from DSMB. The Sponsor and DSMB will assure that confidentiality of the data will be maintained.

If a DSMB recommendation is implemented, the Chairperson of the DSMB will receive written notification of this fact. If the Sponsor does not implement a recommendation, the reasons for such a decision will be documented in writing and provided to the DSMB Chairperson. The Sponsor will assume the responsibility to notify the regulatory agencies of all recommendations of the DSMB.

If the DSMB recommends stopping the trial and the Sponsor agrees, the Sponsor will inform all regulatory agencies of the decision and notify all Investigational sites. Public disclosure of the decision to stop the trial is entirely at the Sponsor's discretion.

APPENDIX

VIS-2014 Clinical Trial DSMB Member List

XXXXXXXXX, M.D. Ophthalmologist/Optometrist	INSERT ADDRESS & CONTACT INFO
XXXXXXXXX, M.D. Ophthalmologist/Optometrist	INSERT ADDRESS & CONTACT INFO
XXXXXXXXX,	INSERT ADDRESS & CONTACT INFO

APPENDIX 6: ANTERIOR SEGMENT ISCHEMIA (ASI): DETECTION, MITIGATION AND REPORTING

Anterior Segment Ischemia (ASI) is a potentially serious but most often self-limited response to decreased perfusion that even in severe cases generally resolves without sequelae or detrimental effects on vision. The rich collateral blood supply of the anterior segment likely explains its relatively benign common clinical course.

Decreased constriction of the pupil in response to light is the earliest physiological indicator of ASI and serves as a bellwether indicating diminished perfusion. Recovery of perfusion, when it occurs at this mild stage, avoids potential sequelae such as persistent pupillary abnormalities. Monitoring the pupillary reflex in the immediate postoperative period helps prevent progression by allowing prompt intervention to restore perfusion while the condition remains completely reversible.

In this clinical study of the VisAbility Implant, Refocus has adopted digital infrared dynamic pupillometry as a sensitive indicator of neuromuscular disturbance secondary to decreased iris vascular perfusion in the immediate postoperative period. Pupillometry serves the primary purpose of evaluating the impact of surgery on perfusion and allowing for prompt removal of scleral implants from eyes that demonstrate compromised perfusion, thus reversing impaired pupillary function and preventing progressive damage from ischemia.

Clinical Syndrome, Natural History and Severity Grading

ASI represents an acute, generally self-limited response of the anterior segment of the eye to decreased vascular perfusion. While mild cases most often resolve without sequelae, more severe cases may develop persistent pupillary abnormalities and iris atrophy. Though rare, cataract and hypotony have been reported in a few isolated, very severe cases.

The clinical syndrome of ASI was first described in 1954 and has become recognized as an uncommon complication of surgery involving the extraocular muscles.[1] Risk factors for the development of ASI include advanced age, previous extraocular surgery, blood dyscrasias, hypercoagulable states, atherosclerosis, carotid artery disease and thyroid related immune orbitopathy. In the setting of strabismus surgery, these risk factors play a larger role in determining susceptibility to ASI than the number or combination of muscles operated.[2]

Anatomical studies have demonstrated that the anterior ciliary arteries are the source of 70 to 80% of the circulation of the anterior segment, including the iris and ciliary body. The long posterior ciliary arteries provide the remainder, along with some contribution from the conjunctiva.[3] The anterior ciliary arteries run along the rectus muscles, dividing into multiple branches and forming three levels of collateral anastomoses near the muscles' scleral insertion points. This rich collateral circulation likely explains the rarity and generally self-limited nature of postoperative ASI.

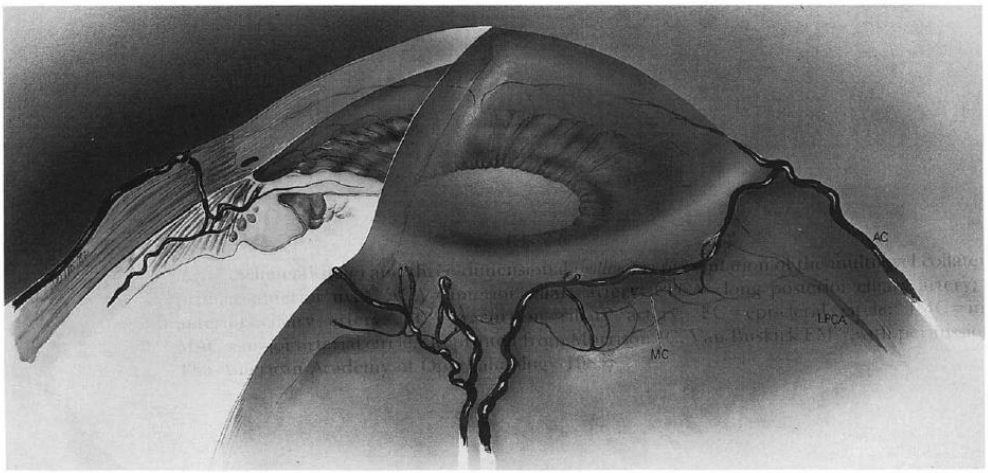


Fig. 3. Schematic (*top*) and three-dimensional (*bottom*) representation of the multilevel collateral circulation in the primate anterior uvea. ACA = anterior ciliary artery; LPCA = long posterior ciliary artery; PACA = perforating anterior ciliary artery; RCA = recurrent ciliary artery; EC = episcleral circle; IMC = intramuscular circle; MAC = major arterial circle. (Reprinted from Morrison JC, Van Buskirk EM[65] with permission of the authors and The American Academy of Ophthalmology 1983)

Delayed perfusion of the iris as demonstrated by angiography is recognized as Grade 1 ASI.[4] However, iris fluorescein angiography is not a useful tool in predicting which patients are likely to progress to higher grades of ASI or develop long-term sequelae postoperatively.[9] Acutely decreased pupil reactivity represents Grade 2 ASI. Anterior chamber reaction in addition to decreased pupil reactivity constitutes Grade 3. Striate keratopathy, which is similar to the type of corneal edema typically seen following cataract surgery, in addition to anterior chamber reaction and decreased pupil reactivity represents the highest level of severity, Grade 4.

Patients with Grade 4 ASI typically experience pain and reduced visual acuity beginning one or two days after surgery. Without any surgical re-intervention, a period of gradual clinical improvement follows, with return of preoperative visual acuity in nine weeks or less.[9] It is not known whether medical treatment with topical or systemic anti-inflammatory agents has any effect on the natural history of ASI. Patients with severe iris ischemia may develop iris atrophy, decreased pupil reactivity and an oval or irregular pupil.

Case reports and series in the literature reveal the natural history typical of ASI. For example, Forbes reported on a case of Grade 4 ASI occurring after a four muscle operation. Striate keratopathy initially reduced the visual acuity to 20/200. Over two months the vision improved to 20/30. Iris atrophy and an irregular pupil were the only sequelae.[5] Keech et al described a case of Grade 4 ASI following a transposition procedure in a 74 year old woman with hypertension. On postoperative day 1, visual acuity was reduced to 20/100. Slit lamp exam revealed an oval pupil with an atonic sphincter, anterior chamber reaction and striate keratopathy. By 6 weeks all clinical signs had resolved except for a sluggishly reactive, oval pupil.[6]

Saunders et al reported on a series of cases involving surgery on three extraocular muscles.[7] Five adult patients developed acute ASI, including 3 with pupil signs and anterior chamber reaction (Grade 3) and 2 with striate keratopathy (Grade 4). Treatment consisted of topical and systemic steroids. With the exception of corectopia, there was complete resolution of all signs within 9 weeks postoperatively. No patient suffered permanent visual loss. Olver and Lee reported a series including 17 eyes with Grade 1, 11 eyes with Grade 2 and 5 eyes with Grade 3 ASI.[16] Recovery of the iris circulation in most patients occurred within 4 weeks of surgery. Only 2 eyes in the entire series demonstrated long-term pupil changes; the remaining eyes had no sequelae.

To further elucidate the natural history of ASI, Bagheri et al investigated ASI in a rabbit model, chosen for its anatomic similarity to the human, including the significant contribution of the vasculature of the 4 rectus muscles to nourishment of the anterior segment.[8] Performing various combinations of surgery involving from 1 to 4 muscles, they found that 51 eyes (30.4%) developed signs of ASI, but in most cases inflammation and corneal edema resolved spontaneously and histopathology revealed no major permanent ischemic changes. Long-term complications included pupil irregularity and decreased response to light in 12 eyes and cataract in 4 eyes. A single case in the 4-muscle group showed neovascularization of the cornea and iris. These findings support the clinically recognized natural history of ASI, which involves complete resolution without sequelae in most cases.

Digital Pupillometry

Because pupillary dysfunction constitutes the earliest functional sign of ASI, sensitive and precise measurement of the pupillary response to light in the immediate postoperative period represents a useful indicator of the risk of disease progression. Other methods of detecting changes in anterior segment perfusion, including iris angiography and laser Doppler flowmetry, have not been proven as useful. Iris angiography is not a useful tool for predicting which patients may develop clinical signs of decreased perfusion; therefore, iris angiography has not been standardized as a means of assessing postoperative iris perfusion, nor has it been utilized to assess the risk of sequelae.[9] In addition, iris angiography does not reveal filling of intrastromal vessels in eyes with highly pigmented irides. Further, the dye pattern is different in each individual, with a wide range of normal filling times and patterns. Additionally, validated commercial instruments designed specifically for iris angiography are not currently available, so iris angiography requires modification of existing equipment.[10] Lastly, iris angiography adds risk due to potential reactions to intravenous fluorescein dye and may also prove difficult due to the status of the ocular surface and subjects' reduced ability to comply with the procedure in the immediate postoperative period due to fatigue and residual effects of intraoperative sedation.

While laser Doppler flowmetry has found utility in the study of the retinal and optic nerve head circulation, it has had only limited investigational use for the purpose of measuring the blood flow of the iris in humans.[11,12,13] This technique requires adaptation of a laser delivery system, photodetector and target fixation device to a slit lamp, and while it has been used to investigate the effects of increased intraocular pressure and increased arterial pressure on perfusion, it has not to date been used to investigate the impact of reduced blood flow in the anterior ciliary arteries.[14]

Therefore, digital infrared dynamic pupillometry is the optimal indicator of iris neuromuscular function relative to iris vascular perfusion. Measurement of the dynamic response of the pupil to standardized illumination is the most sensitive means to assess the eye's recovery from surgery because pupillary abnormalities represent the earliest functional sign of anterior segment ischemia (ASI).[15] The purpose of pupillometry in the immediate postoperative period in this study is to allow for timely removal of scleral implants and prevent the development of potential sequelae.

Infrared digital pupillometry consists of an integrated intense light source for pupil stimulation; an image capture system with an infrared digital camera capable of obtaining pupil measurements throughout the entire examination process (pupil diameter at rest, during light stimulation, and at the end of the stimulus), without interfering with pupil response because it provides no visible light; and a data processor to perform calculations.[16] Using this type of device, i.e., the NeurOptics NPi™-200 Pupillometer (Neuroptics, Inc., Irvine, CA)], the mean percent pupil constriction in a population of healthy adults has been determined to be 34% according to the formula %CH ={[dilated pupil diameter – constricted pupil diameter]/[dilated pupil diameter]} x 100.[17] The authors of this study noted that, "in only one of 2432 measurements was the percentage of reduction below 10%.[17] Therefore, digital infrared pupillometry offers a non-invasive method of obtaining a precise, numerical clinical measurement that serves as an early indicator of risk for progressive ASI and provides a clear threshold criterion value, allowing for timely intervention. Of note, an enrollment criterion for this study excludes any subject in whom the baseline mean percent pupil constriction is less than 30% in either eye, so that any impact of surgery on pupillary function can be readily discerned.

In this protocol we have adopted the following instrumentation, threshold criterion and standard operating procedures:

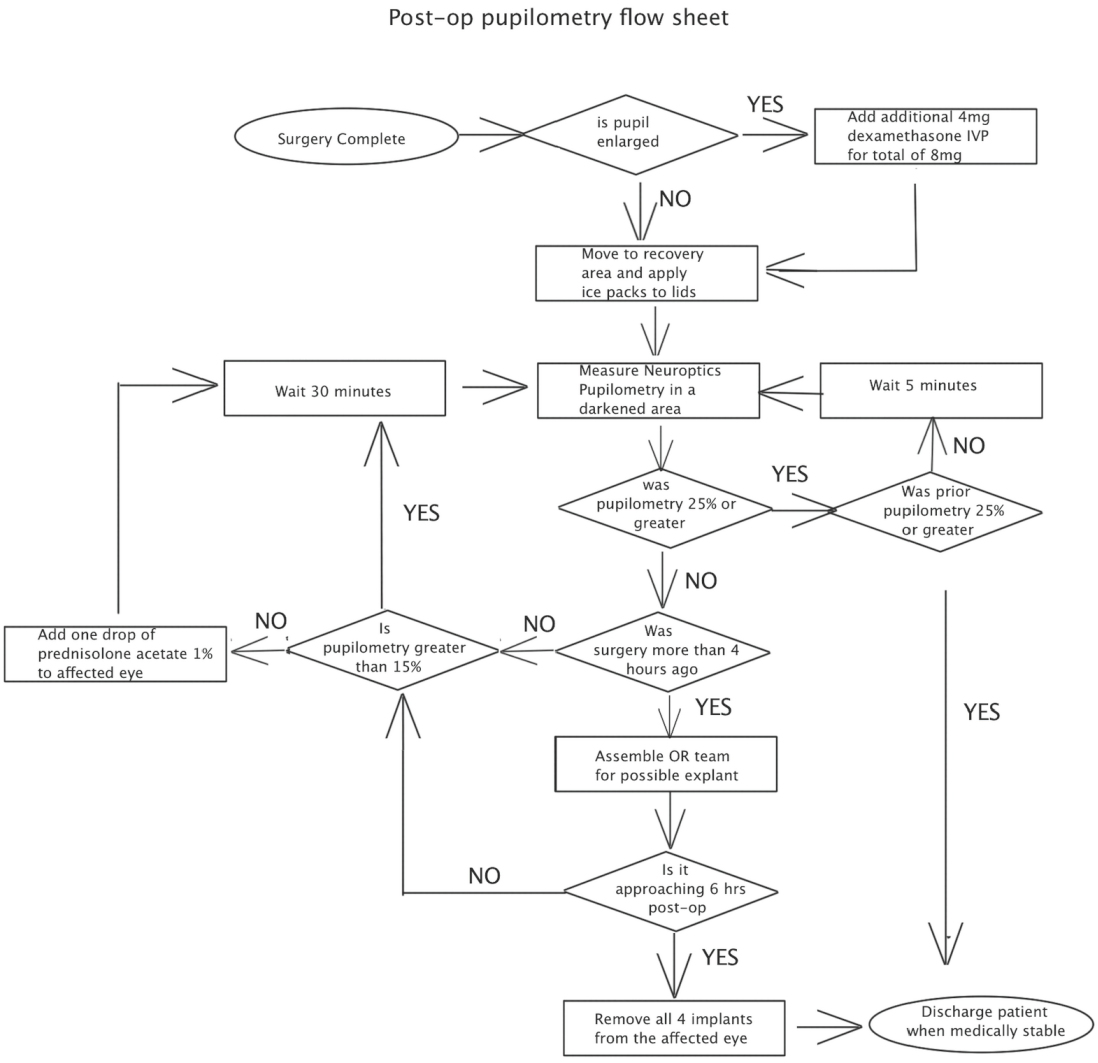
- Measurement of the pupillary reflex in both eyes with the NeurOptics NPi™-200 Pupillometer (Neuroptics, Inc., Irvine, CA)[18] in the immediate post-operative period at 15-30 minute intervals and recording the pupillary reflex in the eye as a percentage constriction based on the following formula:

Percent Change (%CH) = {[dilated pupil diameter – constricted pupil diameter]/[dilated pupil diameter]} x 100

- A threshold criterion value of %CH ≥ 25% constriction in the operative eye at two distinct time points at least 5 minutes apart
- Immediate removal of all PSI from any eye which does not achieve the threshold criterion within 6 hours postoperatively and before the patient is released from the facility; and

- Mandatory electronic reporting of pupil constriction values to Refocus.

This procedure is shown in the flow chart below.



These procedures are designed to allow for timely recognition of persistent reduction in the pupillary reflex and to insure removal of all implant segments from any eye at risk of developing sequelae of ASI prior to discharge of the subject from the surgical facility on the day of surgery.

Adverse Event Reporting

As described above, implant segments are to be removed from any eye with Grade 2 ASI (acutely decreased pupil reactivity) or Grade 3 ASI (decreased pupil reactivity plus anterior chamber reaction) persisting 6 hours postoperative; therefore, the AE category *"Secondary Surgical Intervention: Implant segment removal"* should be reported for these cases. At postoperative day one or later, the constellation of findings of Grade 4 ASI, i.e., corneal edema, anterior chamber

reaction and decreased pupillary reactivity, should be reported with the AE category *"Grade 4 anterior segment ischemia."* Additionally, any persistent pupillary abnormalities due to reduced iris vascular perfusion should be reported with the AE category, *"Pupil abnormalities persisting after 3 months.*"

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[18] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm?lid=83319&lpcd=HLG

APPENDIX 7: SPONSOR COMMITMENTS

Refocus Group, 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 into 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 Investigator's Clinical Agreement will be completed prior to initiation of study at an investigational site.

APPENDIX 8: INVESTIGATOR COMMITMENTS AND RESPONSIBILTIES

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

1. Subject Selection

The investigator is responsible for assuring that all subjects enrolled and determined eligible for the study meet all inclusion and exclusion criteria stated in this protocol.

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 Study Informed Consent in compliance with 21 CFR 50 for each subject, prior to performing surgery on a subject. The original signed Informed Consent Form will be maintained in the subject's medical record, and a redacted copy of the signed Informed Consent Form will become an integral part of each Case Report file provided to the Sponsor.

3. Institutional Review Board (IRB) Approval

The investigator will obtain or verify approval for his/her participation in this study from the IRB for the institution at which the procedure will be performed, prior to enrolling any subjects in the study. The Informed Consent document to be used must also be approved by the IRB prior to initiation of the study.

4. Subject Evaluations and Data Reporting

The investigator is responsible for performing the subject evaluations as described in the study protocol. All information generated by the subject evaluation will be recorded on the subject source document or case report forms. The investigator will sign and date each individual form upon its completion. Originals of all case report forms will be retained in the investigator’s office in order to be available for monitoring by authorized regulatory bodies.

The investigator will not deviate from the study protocol without prior approval from the Sponsor unless protection of the health, safety or welfare of study subjects requires prompt action.

5. Record Retention

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

- 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.
- 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.

6. Investigational Material Accountability

The investigator must maintain accurate records of the receipt, use and return of all investigational devices, including the product identification and serial numbers as applicable. The investigator must assure that study supplies be dispensed only to subjects enrolled and eligible to be in the study and under the direct supervision of the investigator or co-investigators.

The principal investigator must keep records of all investigational supplies. Investigational material accounting procedures must be completed before the study is considered completed.

APPENDIX 9: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983 41st
WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

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 not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. 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."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. 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 current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should 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.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. 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.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described 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, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. 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 change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

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

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

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

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

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, 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, 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.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should 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 should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, 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 population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent 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.

29. 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 population. In such circumstances the physician should 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 should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research 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.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the 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 interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or 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. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.