VIS-2014-5YR

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A PROSPECTIVE, MULTICENTER CLINICAL TRIAL OF THE VISABILITY™ MICRO INSERT SYSTEM FOR THE IMPROVEMENT OF NEAR VISUAL ACUITY IN PRESBYOPIC SUBJECTS - LONG-TERM FOLLOW-UP

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PERSONNEL AND FACILITIES

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LIST OF ABBREVIATIONS

ACD	Anterior Chamber Depth
AE	Adverse Event
BCDVA	Best Corrected Distance Visual Acuity
CRO	Clinical Research Organization
CRF	Case Report Form
D	Diopter
DCNVA	Distance Corrected Near Visual Acuity
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
m	Meter
mm	Millimeters
mm Hg	Millimeters of Mercury
NAVQ	Near Acuity Visual Questionnaire
OD	Right eye
OS	Left eye
PI	Principal Investigator
PMMA	Polymethylmethacrylate
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SPK	Superficial Punctate Keratitis
UADE	Unanticipated Adverse Device Effect
UCDVA	Uncorrected Distance Visual Acuity
UCIVA	Uncorrected Intermediate Visual Acuity
UCNVA	Uncorrected Near Visual Acuity
USA	United States of America
VMI	VisAbility™ Micro Insert
VMIS	VisAbility™ Micro Insert System

VIS-2014-5YR

THREE YEAR ADDITIONAL FOLLOW-UP OF SUBJECTS PREVIOUSLY COMPLETING TWO YEAR PARTICIPATION IN PROTOCOL VIS-2014

1.0 STUDY OUTLINE

1.1 STUDY OBJECTIVE

The objective of this study is to obtain an additional 36 months of safety and effectiveness data from all subjects who were implanted or explanted in Protocol VIS-2014, a prospective, multicenter clinical trial of the VisAbility™ Micro Insert System in presbyopic emmetropes.

1.2 INDICATIONS FOR USE

The VisAbility Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to 1.00 D of refractive cylinder in both eyes and require a minimum near correction of at least +1.25 D reading add.

1.3 SUBJECT POPULATION

Subjects who were implanted or explanted with the VisAbility™ Micro Insert in Protocol VIS-2014 will be invited to participate.

Each subject will be contacted and asked to participate in this follow-up study. Three documented attempts will be made by either regular mail, phone call, text, or email to contact each subject.

Once contacted, study staff will explain the study purpose, procedures, and responsibilities to each potential participant. Subjects who agree to participate must sign the informed consent, be able to understand the study requirements, be willing to follow study instructions, and agree to return for required follow-up visits.

If all three attempts to contact the subject are unsuccessful, a certified letter will be sent to the last known address of the subject and a copy of the certified letter will be retained at the study site. If there is no response from the subject over the course of the study, he/she will be deemed not enrolled at the close of the 60-month window.

1.4 STUDY DESIGN

VIS-2014-5YR is a multicenter, observational study to evaluate the long-term safety of the VisAbility Micro Inserts in subjects who were implanted or explanted with the VisAbility™ Micro Insert in the VIS-2014 clinical trial. Study subjects will be examined at 36-, 48-, and 60-months post-operatively (based on the anniversary of their first VisAbility™ surgery) with no planned interventions. Subjects who opt to have all implant segments bilaterally removed (explanted) after enrollment in VIS-2014-5YR will be followed for 2 years post removal, up to a maximum of 5 years follow-up. Additional visits may include but are not limited to examination at day 1, week 1, month 1, and 2 annual visits, post removal.

1.5 SAMPLE SIZE

All subjects who were implanted or explanted with the VisAbility Micro Insert will be invited to participate. Actual sample size will be determined at the completion of enrollment.

1.6 DATA ANALYSES

Descriptive statistics and summaries will be provided for primary eyes and all eyes for the following:

Primary safety outcomes:

- Partial explantation (1–3 Micro inserts per eye) or complete explantation (4 Micro inserts per eye) and reason(s)
- Anterior Segment Ischemia (Grades 2 – 4)
- Segment exposure due to conjunctival and/or scleral erosion
- Rate of serious adverse events (SAEs)

Secondary safety outcomes:

- Best Corrected Distance Visual Acuity (BCDVA)
- IOP increase > 10 mm Hg over baseline or IOP > 30 mm Hg
- Slit Lamp findings
- Fundus exam findings
- Rate of adverse events (AE's)

Secondary effectiveness outcome:

- Change in uncorrected and distance corrected near visual acuity and letters correct in the primary eye of bilaterally implanted subjects (with all eight implants in place), as compared to baseline (VIS-2014).

1.7 CLINICAL PARAMETERS

The following clinical parameters will be measured:

- Near visual acuity (uncorrected, distance corrected)
- Distance visual acuity (uncorrected and best corrected)
- Intermediate visual acuity (uncorrected)
- Patient Preferred Distance
- Minimum add to 20/20
- Dynamic pupillometry
- Corneal Topography/Keratometry
- Manifest refraction
- IOP
- Slit lamp biomicroscopy
- Indirect Ophthalmoscopy
- Cup/Disc Ratio

A full description of the examination schedule and clinical parameters for the entire 5-year study can be found in Table 1.

TABLE 1: SCHEDULE OF VISITS AND MEASUREMENTS

		Initial								VIS-2014 Follow-up		VIS-2014-5YR Follow-up		
	Pre-Op	0 Day	1 Day	1 Wk	1 Mo	2 Mo	3 Mo	6 Mo	12 Mo	18 Mo	24 Mo	36 Mo	48 Mo	60 Mo
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	✓											✓	✓	✓
Dynamic 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	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BCDVA OD, OS, OU	✓[2]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
UCDVA OD, OS, OU	✓		✓[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
UCNVA @ 40 cm OD, OS, OU	✓						✓	✓	✓	✓	✓	✓	✓	✓
UCIVA @ 66 cm OU	✓						✓	✓	✓	✓	✓	✓	✓	✓
DCNVA @ 40 cm OD, OS, OU	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient Preferred Distance DCN - OD, OS, OU	✓						✓	✓	✓	✓	✓	✓	✓	✓
Minimum add to 20/20	✓						✓[3]	✓[3]	✓[3]	✓[3]	✓[3]	✓	✓	✓
NAVQ (Validated PRO) & Subject 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.

2.0 INTRODUCTION & RATIONALE

The VisAbility™ Micro Insert is a curved scleral implant that is injection molded from polymethylmethacrylate (PMMA), a material with an extensive history of use in permanent implants in the human eye, including intraocular lenses (IOLs). Four VisAbility™ Micro Inserts are placed in a single presbyopic eye to improve near vision.

Each VisAbility™ Micro Insert consists of 2 pieces, a main body segment with 2 legs and a locking segment. The locking segment has trans-longitudinal grooves on both sides that correspond to 2 small "rails" on the interior edges of the legs of the main body segment (**Figure 1**). These features allow the locking segment to be smoothly snapped into place in the main body segment. The design of the VisAbility™ Micro Inserts include stabilization feet at each end intended to fixate at the entrance and exit sites of the scleral tunnel incision, thereby preventing displacement or migration of the implanted VisAbility™ Micro Insert. The VisAbility™ Micro Inserts are provided sterile in a Tyvek® peel pouch.

Figure 1
VisAbility™ Micro Insert Showing 2 Interlocking Pieces and Stabilization Feet

Each VisAbility™ Micro Insert is implanted in a scleral tunnel approximately 4.0 mm posterior to the corneal limbus through scleral incisions centered at the 1:30, 4:30, 7:30, and 10:30 o'clock oblique quadrants. **Figure 2** shows a human eye model implanted with four VisAbility™ Micro Inserts.

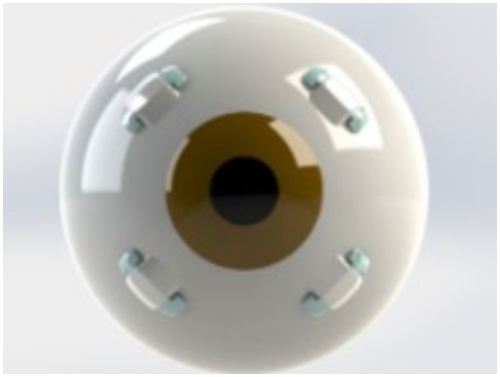

FIGURE 2
PLACEMENT OF THE VISABILITY™ MICRO INSERTS

3.0 SUBJECT POPULATION

Subjects who participated in the VIS-2014 clinical trial.

3.1 INCLUSION CRITERIA

- Subjects must have been implanted or explanted with the VisAbility™ Micro Insert in the VIS-2014 clinical trial.
- Subjects must be alert, mentally competent, and able to understand and comply with the requirements of the clinical trial and be personally motivated to abide by the requirements and restrictions of the clinical trial.
- Subjects must provide written informed consent.

3.2 EXCLUSION CRITERIA

- Subjects who do not wish to participate or do not provide written informed consent.

4.0 INVESTIGATIONAL PROCEDURES

4.1 SUBJECT ENTRY

4.1.1 SUBJECT CONTACT

Each subject will be contacted and asked to participate in this follow-up study. Three documented attempts will be made by either regular mail, phone call, text, or email to contact each subject.

Once contacted, study staff will explain the study purpose, procedures, and responsibilities to each potential participant. Subjects who agree to participate must sign the informed consent, be able to understand the study requirements, be willing to follow study instructions, and agree to return for required follow-up visits.

If all three attempts to contact the subject are unsuccessful, a certified letter will be sent to the last known address of the subject and a copy of the certified letter will be retained at the study site. If there is no response from the subject over the course of the study, he/she will be considered not enrolled at the close of the 60-month window.

4.1.2 INFORMED CONSENT

Written informed consent will be obtained for all subjects who agree to enroll in VIS-2014-5YR. Subjects may be consented and enrolled at any time between the opening of the 36-month window and the close of the 60-month window.

4.1.3 SUBJECT REFUSAL, INABILITY TO PARTICIPATE, OR INABILITY TO CONTACT

If a subject refuses participation, or is unable to participate in the study, the reason for refusal or inability to participate will be documented. Documentation will also be retained for subjects who could not be contacted.

4.2 EXAMINATION SCHEDULE

Visit windows are calculated based on a 30-day month. The visit windows are based on the anniversary of the first VisAbility surgery. The examination schedule is as follows:

- Month 36 (+/- 60 days postoperative)
- Month 48 (+/- 60 days postoperative)
- Month 60 (+/- 60 days postoperative)

Subjects may be consented and enrolled at any time between the opening of the 36-month window and the close of the 60-month window. Visit data for subjects examined between visit windows for the 36, 48, and 60 month exam will be considered out-of-window.

Subjects who opt to have all implant segments bilaterally removed (explanted) after enrollment will be followed for 2 years post removal, up to a maximum of 5 years follow-up. Additional visits may include but are not limited to examination at day 1, week 1, month 1, and 2 annual visits, post removal.

4.3 CLINICAL PARAMETERS

The following clinical parameters will be measured:

- Near visual acuity (uncorrected, distance corrected)
- Distance visual acuity (uncorrected and best corrected)
- Intermediate visual acuity (uncorrected)
- Patient Preferred Distance
- Minimum add to 20/20
- Dynamic pupillometry
- Corneal Topography/Keratometry
- Manifest refraction
- IOP
- Slit lamp biomicroscopy
- Indirect Ophthalmoscopy
- Cup/Disc Ratio

A full description of the examination schedule and clinical parameters are referenced in Table 1.

4.4 DATA COLLECTION

Sample paper source documents will be provided by the Sponsor, Refocus Group, Inc. (Refocus) for each subject enrolled in the study and may be completed by the Investigator or Sub-Investigator at the time of the subject examination. The source documents should 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 corrections 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 validated database will be equivalent to that used for the VIS-2014 trial. Study data will be maintained on a secure computer with appropriate data security provisions. 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.

4.5 STUDY COMPLETION PROCEDURES

4.5.1 SUBJECT COMPLETION

Subjects are considered to have completed the study if they have completed the 60-month exam, or the 60-month visit window has closed.

4.5.2 SUBJECT TERMINATION

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. Furthermore, every effort will be made in all instances to conduct examinations as determined by the Investigator to ensure the safety of the subject. The Sponsor shall be

notified promptly by the Investigator/study staff upon the termination or withdrawal of a subject by completion of the Study Exit form. Subjects who opt to have all implant segments bilaterally removed (explanted), after enrollment in VIS-2014-5YR, will be followed for 2 years post removal, up to a maximum of 5 years follow-up. Additional visits may include but are not limited to examination at day 1, week 1, month 1, and 2 annual visits, post removal.

4.5.3 SUBJECT EXIT

A subject exit form must be completed for all subjects who either complete, discontinue, are lost to follow-up, or are terminated from the study.

5.0 STATISTICAL METHODS

5.1 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, Revision 018, Section B.5.3, as modified and explained below:

- Enrolled – the total number of subjects enrolled (consented) in the study.

- Discontinued – Subjects (eyes) that have discontinued treatment prior to the visit window associated with the form, as a result of death, or any other reason except lost to follow-up.

- Lost to Follow-up – Subjects that have withdrawn from the study after enrollment, 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.

5.2 STATISTICAL ANALYSIS

Due to the observational, non-comparative nature of this study, the statistical analysis will be based on descriptive statistics. Summary statistics will be provided for all primary and secondary outcomes (listed above in Section 1.6) for primary and all eyes.

All subjects enrolled will be included in the data analyses. Visit data for subjects examined between visit windows for the 36, 48, or 60 month exam will be considered out-of-window. Missing data will only be imputed for observations that occur after enrollment into the study. In the absence of observed data between 36 months and including 60 months, the missing data will be imputed using trends seen in subjects with available data using data recorded between and including the 36-month visit up to the 60-month visit (including out of window). Scientific evidence and rational for those trends and imputation methodology will be provided in the report of the final analysis. Imputation may include but is not limited to; best/worst case analysis, multiple imputation or tipping point analysis (for binary outcomes).

Analysis will contain primary implanted eyes (dominant eye), fellow implanted eyes, and bilateral (OU) data where appropriate. Analysis will include all implanted and explanted eyes (OD, OS).

5.3 ANALYSIS OF CLINICAL PARAMETERS

Means, standard deviations, and ranges (min/max) will be derived from the continuous measurements. Frequencies, rates (cumulative incidence), and proportions will be used for summarizing the categorical and ordinal outcomes.

6.0 ADVERSE EVENT REPORTING

An Adverse Event (AE) is any untoward sign, symptom or disease observed during 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.

6.1 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 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 and requires intervention to prevent permanent impairment or damage.
- It requires or prolongs inpatient hospitalization. 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) or impairment of a body function or damage to body structures.
- 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.

6.2 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 serious adverse effect on health or safety within 24 hours of observing or learning of the event. The sponsor will monitor and evaluate all study AEs to ensure the collective nature, severity, and degree of incidence is measured. Refocus will be responsible for informing the appropriate Regulatory Authorities, IRBs, and Investigators participating in the study of the UADE.

6.3 ADVERSE EVENT ASSESSMENT

All study subjects 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 the 36-month exam 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, and
- 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 ⇒ fainting and fall to floor ⇒ head trauma ⇒ neck pain

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

6.4 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.

6.5 CLASSIFICATION OF ADVERSE EVENTS BY EXPECTEDNESS/RELATEDNESS

All AEs will be evaluated as to whether they are expected or unexpected. The sponsor will monitor and evaluate all study AEs to confirm the appropriate assignment of classification based on the collective nature, severity, and degree of incidence.

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 has a cause other than the investigational device (e.g. pre-existing condition or underlying disease, concurrent illness, or concomitant medication).

Possibly Related: There is a temporal association with the investigational device and it cannot be excluded as a cause, but other etiologies could possibly 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.

6.6 ADVERSE EVENT OUTCOME

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

- Resolved, i.e., all signs and symptoms of the adverse event have resolved without sequelae and all medications or treatment have been discontinued.
- Resolved with Continuing Treatment, i.e., all signs and symptoms of the adverse event have resolved, although treatment may be ongoing at the time of study discontinuation.
- Resolved with sequelae (specify), i.e., at least one sign and/or symptom referable to the adverse event is still present at the time of study discontinuation.
- Ongoing, i.e. the adverse event is ongoing at the time of study discontinuation.
- Death.

6.7 TREATMENT OR ACTION TAKEN

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

- None,
- Medical Intervention,
- Surgical Intervention, and/or
- Other

6.8 POSSIBLE ADVERSE EVENTS

Possible 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., 36 months means the 36-month postoperative visit).

These specific examples of possible Adverse Events for VIS-2014-5YR include, but are not limited to:

Lids and Lashes

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

Cornea

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

Conjunctiva/Sclera

- Conjunctival cyst
- Conjunctival erosion
- Moderate or severe conjunctival injection
- Subconjunctival hemorrhage (not associated with an explant or concomitant procedure)
- Conjunctivitis (allergic, bacterial, viral)
- Scleral erosion
- Scleritis

Anterior Segment, Iris, Lens

- Persistent pupil abnormalities
- Posterior Synechiae
- Rubeosis Irides
- Anterior segment ischemia (Grades 2 – 4)
  - Grade 2: Decreased pupil reactivity (%CH < 25%)
  - Grade 3: Decreased pupil reactivity plus anterior chamber reaction (Grade 2 with cell and/or flare)
  - Grade 4: Corneal edema, anterior chamber reaction and decreased pupillary reactivity (Grade 3 with striate keratopathy)
- Anterior chamber cells or flare
- Intraocular Inflammation other than anterior chamber cells and flare (e.g. Vitritis)
- Two grade change in lens opacity as compared to preoperative baseline

Implants

- Displaced, extruded, or missing implant segments

Intraocular Pressure

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

BCDVA Loss

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

Fundus

- Choroidal effusion
- Retinal detachment
- Retinal or vitreous hemorrhage
- Retinal hole
- Posterior vitreous detachment

Secondary Surgical Intervention

- Implant segment removal
- Exposed implant segments or conjunctival retraction requiring conjunctival re-approximation
- Cataract extraction
- Any other secondary surgical intervention

Other

- Eye pain requiring oral prescription pain medication
- Allergic reactions to medications, devices, sutures or anesthesia
- Other findings indicating a worsening of two grades (i.e. grade +3 or +4), as compared to the initial VIS-2014 5YR baseline

7.0 MONITORING

Sponsor or CRA personnel will monitor all clinical studies in a manner consistent with FDA guidelines. Study monitoring will involve the following elements:

- Sponsor or CRO personnel will meet with Investigators prior to the initiation of the VIS-2014-5YR 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.

8.0 REFERENCES

1. 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.

2. 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].

3. ANSI Z80.29-2015 - Ophthalmics - Accommodative Intraocular Lenses

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). Sites should maintain dim room illumination throughout the testing sequence and during manifest refraction and FVA/OPTEC acuity testing, and care should be taken to avoid light shining on the lenses of the FVA/OPTEC or on the subject's face. All distance-corrected acuities (BCDVA, DCNVA) will be tested using a trial frame and subjects shall be visually observed and verbally reminded not to squint during all distance and near acuity measurements.

Manifest Refraction

Manifest refraction will be performed using Lombart CVSI21 computerized acuity systems and all recorded visual acuities will be measured via the Functional Vision Analyzer (FVA)/OPTEC 6500.. All systems will employ actual or equivalent optical distances of at least 20 feet and ambient lighting will be adjusted to be dimmer than the chart. Chart luminance will fall within the ANSI required range of 80-160 cd/m^2 and chart contrast will be a minimum of 85%. The final manifest refraction will be confirmed in a trial frame, after testing in the phoropter.

Instruments for Measuring Visual Acuities

Manifest refraction will be determined using the Lombart CVSI21 computerized acuity system and all recorded visual acuities will be measured via the Functional Vision Analyzer (FVA)/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 FVA/Optec 6500 system utilizes a lens system to simulate various test distances for distance, intermediate, and near. The FVA/Optec 6500 has a microprocessor controlled internal illumination system that results in constant luminance of 85 cd/m^2; therefore, dim ambient lighting will be used. 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 6 m (~20 ft.).

Intermediate Visual Acuity

Intermediate visual acuity will be measured at a simulated (optical) distance of 66 cm (~26 in.).

Near Visual Acuity

Near visual acuity will be measured at a simulated (optical) distance of 40 cm (~15.75 in.).

Patient Preferred Distance

Patient preferred distance will be measured monocularly and binocularly (OD, OS, OU) thru the manifest refraction. The Cal light meter, a tape measure, and an ETDRS VA flip chart are required.

- Place the patient's manifest refraction into a trial frame.
- Have the subject hold an ETDRS VA flip chart at 40 cm from the spectacle plane of the trial frame.
- Hold the Cal light meter at the plane of the ETDRS VA flip chart to ensure that the illumination falls between 250-284 lux.
- Identify the visual acuity line that corresponds with the threshold DCNVA obtained with the Optec/FVA instrument.
- Have the subject cover one eye with an occluder and ensure the subject can read the line.
- Then, have the subject adjust the reading distance of the flip chart via a "tromboning" motion until they determine the distance at which the VA line appears clearest to them. Remind the subject that it may be closer or further away than the initial starting point (40 cm).
- When the subject has determined the clearest distance, measure the distance from the spectacle plane in cm, using a tape measure and round to the nearest whole number.
- Repeat the entire above process for the contralateral eye and then with both eyes together (OU).
- Record all three distances on the source document.

Determination of Minimum Add to 20/20
Minimum add will be measured at a simulated distance of 40cm and will be determined by adding plus lenses monocularly until 20/20 is achieved.

Dynamic Pupillometry

Measurement of the pupillary reflex in both eyes will be conducted with the NeurOptics Pupillometer (Neuroptics, Inc., Irvine, CA) at each postoperative visit.

Prior to testing, stimulus intensity should be set to 180μW (microwatts) and stimulus duration should be set to 802msec (milliseconds). To get maximum pupil size, be sure to dark adapt the subject in a completely dark room for at least 3 minutes (as described on Page 16 of the Neuroptics Pupillometer Instruction Manual). Before the scans are initiated, a flexible, contoured cup is used to reduce the possibility of stray light entering the eye. During the initial phase of the scan, the maximum pupil size is measured without visible light (0μW) using only infrared lighting thereby maintaining the dark adapted (0μW) lighting conditions. During the next phase of the scan, the pupillometer captures and analyzes a rapid sequence of digital images then stimulates the eye with a flash of light at an intensity of 180μW to measure minimum pupil size. At the end of the measurement sequence, the following scan results will display (as described on Page 21 of the NeurOptics Pupillometer Instruction Manual):

- The intensity (180μW) and duration (802msec) of the light stimulus

- MAX (maximum pupil size) which represents the diameter of the pupil just before constriction
- MIN (minimum pupil size) which represents the diameter of the pupil at the peak of constriction
- LAT (latency) which represents the time of the onset of constriction
- CON (percent constriction) is the percent of the constriction based on the following formula:

  {[MAX pupil diameter – MIN pupil diameter]/[MAX pupil diameter]} x 100

Pupil shape: The pupil shape of both eyes will be assessed at each and every visit as part of the slit lamp examination as follows:

- 1 = round
- 2 = elliptical
- 3 = irregular

Topography/Keratometry

All topography/keratometry measurements will be taken using an automated, commercial grade topographer. All systems will have the capability to map the surface curvature of the cornea**,** using non-invasive imaging. Central keratometry will be measured and the K values will be recorded. Topography will be captured to rule out corneal irregularities.

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
- Trace
- Mild
- Moderate
- Marked or Severe

Corneal abrasion:

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

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 6% 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 guttata:

- 0 = no corneal guttata
- 1 = rare corneal guttata
- 2 = few corneal guttata
- 3 = many corneal guttata
- 4 = marked/severe corneal guttata 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

Conjunctival erosion:

- Absent
- Present

Scleral erosion:

- Absent
- Present

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

Implant Assessment

- Missing Segments = segment is not present
- Shallow segments = segment is closer to the surface and the contour of the implant is easily seen
- Deep segments = segment is barely visible and little to no contour of the implant is seen
- Non-tangential = segment is not equidistant from the limbus
- Tilted segments = one end of the segment is higher than the other
- Too close = segments < 3mm from the limbus
- Too far = segments > 4mm from the limbus
- Exposed Segments = overlying conjunctiva is not present
- Extruded Segments = segment is protruding from the scleral tunnel

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	0 (None)
0.5+	1-5 (Faint)
1+	6-15 (Mild)
2+	16-25 (Moderate)
3+	26-50 (Marked)
4+	50+ (Severe)

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 = Diffuse atrophy
- 3 = Segmental atrophy
- 4 = Sectoral contraction
- Other abnormal iris findings

Assessment of Anterior Segment Ischemia

- Grade 2: Decreased pupil reactivity (%CH < 25%)
- Grade 3: Decreased pupil reactivity plus anterior chamber reaction (Grade 2 with cell and/or flare)
- Grade 4: Corneal edema, anterior chamber reaction and decreased pupillary reactivity (Grade 3 with striate keratopathy)

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.

Posterior Segment Examination

Posterior segment examination should include a full dilated fundus examination and will be assessed using a 20D condensing lens. Abnormalities of any of the structures in any location of the fundus should be noted. Examination may include but is not limited to: vitreous body, optic disc, vasculature, macula, and periphery.

Peripheral Fundus Examination

- Normal
- Abnormal (if abnormal, please describe)

Cup to Disc Ratio will be assessed by means of a fundus exam using condensing lenses (78 D/90 D) 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.

APPENDIX 2: 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 Micro Insert, 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.

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1 Wilson WA, Irvine SR. Pathologic changes following disruption of blood supply to iris and ciliary body. Trans Am Acad Ophthalmol Otolaryngol. 1955 Jul-Aug;59(4):501-2.

2 Hiatt RL. Production of anterior segment ischemia. Trans Am Ophthalmol Soc. 1977;75:87-102.

3 Wilcox LM, Keough EM, Connolly RJ, Hotte CE. The contribution of blood flow by the anterior ciliary arteries to the anterior segment in the primate eye. Exp Eye Res. 1980 Feb;30(2):167-74.

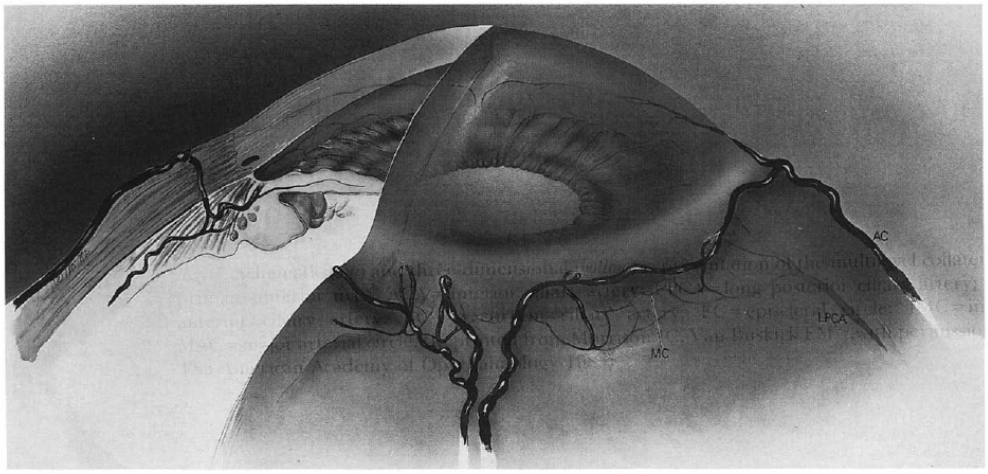

Fig. 3. Schematic (*top*) and three-dimensional (*bottom*) representation of the multilevel collateral circulation in the primate anterior uvea. ACA = anterior ciliary artery; LPCA = long posterior ciliary artery; PACA = perforating anterior ciliary artery; RCA = recurrent ciliary artery; EC = episcleral 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]

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[4] Olver JM, Lee JP. The effects of strabismus surgery on anterior segment circulation. Eye (Lond). 1989;3 (Pt 3):318-26.

[5] Forbes SB. Muscle Transplantation for External Rectus Paralysis : Report of Case with Unusual Complications. Am. J. Ophth. 48:248-251 (Aug.) 1959.

[6] Keech RV, Morris RJ, Ruben JB, Scott WE. Anterior segment ischernia following vertical muscle transpositionand botulinum toxin injection (letter) . Arch Ophthalmol 108:176, 1990.

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.[15] 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.

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[7] Saunders RA, Phillips MS. Anterior segment ischemia after three rectus muscle surgery. Ophthalmology. 1988 Apr;95(4):533-7.

[8] Bagheri A, Tavakoli M, Torbati P, Mirdehghan M, Yaseri M, Safarian O, Yazdani S, Silbert D. Natural course of anterior segment ischemia after disinsertion of extraocular rectus muscles in an animal model. J AAPOS. 2013 Aug;17(4):395-401.

[9] Saunders RA, Bluestein EC, Wilson ME, Berland JE. Anterior segment ischemia after strabismus surgery. Surv Ophthalmol. 1994 Mar-Apr;38(5):456-66.

[10] Brancato R, Bandello F, Lattanzio R. Iris fluorescein angiography in clinical practice. Surv Ophthalmol. 1997 Jul-Aug;42(1):41-70.

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.

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[11] Chamot SR, Movaffaghy AM, Petrig BL, Riva CE. Blood flow in the human iris measured by laser Doppler flowmetry. Microvasc Res. 1999 Mar;57(2):153-61.

[12] Chamot SR, Movaffaghy A, Petrig BL, Riva CE. Iris blood flow response to acute decreases in ocular perfusion pressure: a laser Doppler flowmetry study in humans. Exp Eye Res. 2000 Jan;70(1):107-12.

[13] Michelson G, Groh M, Gründler A. Regulation of ocular blood flow during increases of arterial blood pressure. Br J Ophthalmol. 1994 Jun;78(6):461-5.

[14] Riva CE, Geiser M, Petrig BL; Beijing 100193, PR China. Ocular Blood Flow Research Association. Ocular blood flow assessment using continuous laser Doppler flowmetry. Acta Ophthalmol. 2010 Sep;88(6):622-9.

[15] Olver JM, Lee JP. Recovery of anterior segment circulation after strabismus surgery in adult patients. Ophthalmology. 1992 Mar;99(3):305-15.

[16] Martínez-Ricarte F, Castro A, Poca MA, Sahuquillo J, Expósito L, Arribas M, Aparicio J. Infrared pupillometry. Basic principles and their application in the non-invasive monitoring of neurocritical patients. Neurologia. 2013 Jan-Feb;28(1):41-51.

[17] Taylor WR, Chen JW, Meltzer H, Gennarelli TA, Kelbch C, Knowlton S, Richardson J, Lutch MJ, Farin A, Hults KN, Marshall LF. Quantitative pupillometry, a new technology: normative data and preliminary observations in patients with acute head injury. Technical note. J Neurosurg. 2003 Jan;98(1):205-13.

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

Measurement of the pupillary reflex in both eyes will be conducted with the NeurOptics Pupillometer (Neuroptics, Inc., Irvine, CA) at each postoperative visit.

Prior to testing, stimulus intensity should be set to 180μW (microwatts) and stimulus duration should be set to 802msec (milliseconds). To get maximum pupil size, be sure to dark adapt the subject in a completely dark room for at least 3 minutes (as described on Page 16 of the Neuroptics Pupillometer Instruction Manual). Before the scans are initiated, a flexible, contoured cup is used to reduce the possibility of stray light entering the eye. During the initial phase of the scan, the maximum pupil size is measured without visible light (0μW) using only infrared lighting thereby maintaining the dark adapted (0μW) lighting conditions. During the next phase of the scan, the pupillometer captures and analyzes a rapid sequence of digital images then stimulates the eye with a flash of light at an intensity of 180μW to measure minimum pupil size. At the end of the measurement sequence, the following scan results will display (as described on Page 21 of the NeurOptics Pupillometer Instruction Manual):

- The intensity (180μW) and duration (802msec) of the light stimulus
- MAX (maximum pupil size) which represents the diameter of the pupil just before constriction
- MIN (minimum pupil size) which represents the diameter of the pupil at the peak of constriction
- LAT (latency) which represents the time of the onset of constriction
- CON (percent constriction) is the percent of the constriction based on the following formula:

  {[MAX pupil diameter – MIN pupil diameter]/[MAX pupil diameter]} x 100

Pupil shape: The pupil shape of both eyes will be assessed at each and every visit as part of the slit lamp examination as follows:

- 1 = round
- 2 = elliptical
- 3 = irregular

Adverse Event Reporting

The constellation of findings of Grade 4 ASI, i.e., corneal edema, anterior chamber reaction and decreased pupillary reactivity, should be reported as follows:

- Anterior segment ischemia (Grades 2 – 4)
  - Grade 2: Decreased pupil reactivity (%CH < 25%)
  - Grade 3: Decreased pupil reactivity plus anterior chamber reaction (Grade 2 with cell and/or flare)
  - Grade 4: Corneal edema, anterior chamber reaction and decreased pupillary reactivity (Grade 3 with striate keratopathy)

APPENDIX 3: DATA SAFETY MONITORING BOARD

Per the 01March2006 FDA Guidance document “The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors”, the Data Safety Monitoring Board (the “DSMB”) established by Refocus for the VIS-2014 Clinical Trial will not need to be continued for the three years’ additional follow-up of subjects in protocol VIS-2014-5YR.

APPENDIX 4: SPONSOR COMMITMENTS

Refocus 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 5: INVESTIGATOR COMMITMENTS AND RESPONSIBILTIES

Each Investigator must be a licensed physician who has completed a residency in ophthalmology and had been trained in the VisAbility™ Micro Insert Surgical Procedure. 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 form as indicated on the form upon its completion. Originals of all case report forms will be retained in the investigator’s office to be available for monitoring by the Sponsor or 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.

APPENDIX 6: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964,
amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975,
and the 35th World Medical Assembly, Venice, Italy, October 1983

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association 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 only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research, a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICIAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.