THE HYDRUS MICROSTENT FOR REFRACTORY OPEN-ANGLE GLAUCOMA:

A PROSPECTIVE, MULTICENTER CLINICAL TRIAL

(SUMMIT)

STUDY ID:

CP 16-001

PROTOCOL and STATISTICAL ANALYSIS PLAN

December 2019

NCT03267134

PROTOCOL NCT03267134

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Rev 08-2020

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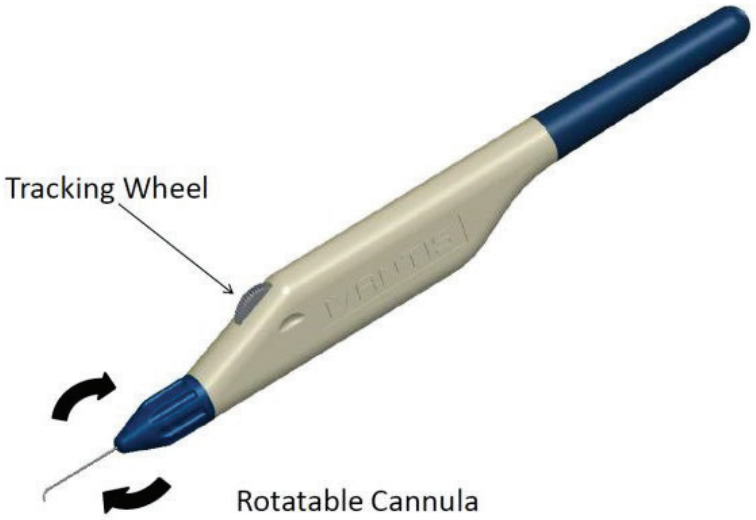
1.0 DEVICE DESCRIPTION

The Hydrus Microstent is a crescent-shaped implantable device pre-loaded onto a hand-held delivery system.

The Hydrus Microstent is composed of nitinol, a metal alloy of nickel (Ni) and titanium (Ti). Nitinol has been used extensively in a variety of implantable vascular and orthopedic devices for its proven properties of flexibility, strength and biocompatibility. As a shape memory alloy, nitinol has super elastic properties making it suitable as a support structure in Schlemm's canal. The Hydrus is approximately 8mm in overall length. The major and minor axes of the implant are 292µm and 185µm, respectively.

The implant is laser cut to a proprietary design with alternating “spines” for structural support and “windows” to provide outflow pathways for aqueous humor. After laser cutting, the shape of the implant is heat-set to a curvature that matches the curvature of Schlemm’s canal and is electro-polished to create a smooth biocompatible surface. The length and curvature of the implant are designed to occupy approximately 90° or 3 clock hours of Schlemm’s canal. The implant is designed to have adequate structural thickness to support the tissue of the canal while providing maximum open flow areas through the canal, with the proximal portion of the implant exiting the canal through the trabecular meshwork to allow inflow of aqueous humor from the anterior chamber.

The **Hydrus Delivery System** is a hand-held mechanical device that provides for manual delivery of the Hydrus Microstent through a stainless steel cannula into the target site in the eye. The delivery system was designed for usability to provide smooth tracking and controlled delivery of the microstent into Schlemm's canal. The hand piece is an ergonomic design for use in either the right or left hand, allowing for surgeon individual preference and hand position. To accommodate a wide range of hand positions, a rotatable sleeve at the distal end allows positioning and alignment of the cannula by the surgeon to direct the implant into Schlemm's canal. The tracking wheel on the delivery system serves as the control mechanism to advance the implant into the canal or retract the implant into the cannula.



To deliver the microstent into Schlemm's canal, the cannula of the delivery system is inserted through a clear corneal incision (approximately 1.5mm in length). The cannula tip is then advanced through the trabecular meshwork until it enters Schlemm's canal and the entry point into the meshwork is coincident with the end of the cannula bevel. The target tissue is visualized using a gonioscopic prism. After observing that the distal cannula tip is properly positioned through the trabecular meshwork into Schlemm's canal, the tracking wheel on the delivery system is used to advance and release the microstent.

The Hydrus Microstent is packaged in sterile-barrier packaging and provided "STERILE" by gamma irradiation.

2.0 SUMMARY OF NONCLINICAL STUDIES

2.1 Biocompatibility Testing

The selection of biocompatibility tests of the Hydrus Microstent was based on guidelines presented in EN ISO 10993-1 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process and ANSI Z80.27-2014- Aqueous Shunts for Glaucoma

Applications (Section 4.2) with specific requirements applicable to metallic or non-polymeric implants as described in ANSI Z80.27, Section 6.3.

The biocompatibility of the Hydrus Microstent and the Hydrus delivery system has been established through studies conducted by Wu-Xi AppTec, Inc. (St. Paul, MN) in accordance Good Laboratory Practices (GLP) and with EN ISO 10993-1 and parts 3, 5, 6, 10 and 11 for specific test requirements. For tests requiring extracts, coupons of nitinol were utilized rather than the Hydrus Microstent itself due to the very small mass and surface area of the Hydrus Microstent. The coupons were made of the same nitinol material and processed in a manner representative of production processes utilized to manufacture the implant, including laser cutting, electropolishing, cleaning and gamma irradiation.

The delivery system is classified as having limited (<24 hours) ocular tissue contact. To demonstrate biocompatibility, cytotoxicity, delayed hypersensitivity, and intracutaneous irritation testing were performed. All results were negative for toxic effects. For the Hydrus Microstent, tested for permanent (>30 days) ocular tissue contact, the following studies were performed: cytotoxicity, material mediated pyrogen, acute systemic toxicity, delayed hypersensitivity, intracutaneous irritation, mutagenicity/genotoxicity, subacute toxicity, subchronic toxicity and muscle implantation (13 weeks). Additionally, a 6-month ocular implantation study was conducted in rabbits. The results of testing on the Hydrus Microstent are summarized in Table 2 below. No biological toxicity was observed in any of the above test systems as identified in the test-specific ISO 10993 standards.

Additionally, chemical characterization of extractables and leachables materials was performed by Legend Technical Services with review and a toxicological risk assessment performed by a qualified expert. These studies demonstrated negligible risk to health due to materials extracted or leached from nitinol samples representative of the implant. A follow-on longer-term nickel elution study by WuXi Apptec using Hydrus Microstent as the test article confirmed the finding of negligible health risk from eluted nickel from the implant.

TABLE 2

RESULTS OF BIOCOMPATIBILITY TESTING ON HYDRUS MICROSTENT

ISO 10993	TEST	RESULT
Part 3	Mutagenicity/Genotoxicity, Bacterial Reverse Mutation Study – saline and DMSO extracts	Non-mutagenic
Part 3	In vitro Mouse Lymphoma Assay – 2 extracts	Non-genotoxic
Part 3	In vivo Mouse Micronucleus Assay – 2 extracts	Non-genotoxic
Part 5	Cytotoxicity Study using ISO Elution Method - MEM	Non-toxic
Part 5	Cytotoxicity Study using ISO Agarose Overlay Method	Non-toxic
Part 6	Muscle Implantation Study (13 weeks)	Non-irritant

Part 6	Chronic Ocular Implantation Study in Rabbits (6 months)	Non-inflammatory Non-toxic
Part 10	Delayed Hypersensitivity (Maximization) Study - saline and sesame oil extracts	Non-sensitizing
Part 10	Intracutaneous Irritation Study - saline and sesame oil extracts	Non-irritant
Part 11	Acute systemic toxicity - saline and sesame oil extracts	Non-toxic
Part 11	Subacute toxicity (intraperitoneal) - sesame oil extract	Non-toxic
Part 11	Subchronic toxicity (intravenous) - saline extract	Non-toxic
Part 11	Material mediated pyrogen (rabbit)	Non-pyrogenic
Part 18	Chemical Hexane Extraction and Saline Leach Study	Negligible risk from extracted/leached materials
Part 18	Nickel Elution Study	Negligible risk from eluted nickel

3.0 STUDY METHODS

3.1 Selection of Patients

Only subjects who meet the inclusion and exclusion criteria will be eligible for surgery in this study.

3.2 Screening Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible. Unless otherwise specified, all ocular criteria refer to the study eye only.

- Male and female patients at least 45 years of age
- A diagnosis of open-angle glaucoma (POAG, PXG, or PG), with optic nerve pathology described by one or more of the following:
    - Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles with or without disc hemorrhage;
    - Localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles; or
    - Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue
- BCVA of 20/80 or better in the study eye
- Subject has refractory glaucoma, defined as:
    - Previously failed filtering or cilioablative procedure (i.e., includes incisional glaucoma surgery, cryotherapy, and cyclodiode therapy) and with uncontrolled IOP on medical therapy

or

- IOP is uncontrolled on maximum tolerable medical therapy (e.g., a minimum of four or more classes of topical glaucoma medications, or fewer if others are not tolerated or are not effective)

- Subject has been on current glaucoma medication regimen for at least 30 days
- A medicated IOP of ≥ 20 mmHg and ≤ 35 mmHg by Goldmann applanation tonometry
- Open anterior chamber angle anatomy (e.g., no peripheral anterior synechiae or iris processes) visualized by gonioscopy with a Shaffer angle grade of ≥ III in all four quadrants
- Visual field examination using Humphrey-Zeiss 24-2 SITA Std., with mean deviation (MD) of -3 dB or worse (conducted within 60 days of Screening is acceptable)
- Visual field defects consistent with glaucomatous optic nerve damage, and with at least one of the following two findings:
  - A cluster of 3 or more points in an expected location of the visual field depressed below the 5% level, at least 1 of which is depressed below the 1% level on pattern deviation (PD) plot
  - Glaucoma hemi-field test "outside normal limits"
- The subject is able to understand the requirements of the study and provide written informed consent
- Subject is willing to follow study instructions, agrees to comply with all study procedures and attend all scheduled follow-up exams for 12 months postoperatively

3.3 Screening Exclusion Criteria

Excluded from the study will be individuals with the following characteristics. Unless specified otherwise, all ocular criteria refer to the study eye only.

- Secondary glaucoma other than pseudoexfoliative and pigmentary (e.g., neovascular, uveitic, traumatic, steroid induced, lens induced, or glaucoma associated with increased episcleral venous pressure)
- Diagnosis of acute angle closure, chronic angle closure, or congenital, malignant, or developmental glaucoma
- Central visual field depression within 5 degrees of fixation with sensitivity < 15 dB in both hemifields on the numerical/dB plot
- Pre-perimetric glaucoma
- Ocular hypertension
- Shallow or flat anterior chamber
- Presence of peripheral anterior synechiae or iris processes obscuring angle visualization
- Central corneal thickness greater than 620 or less than 480 microns
- History of complicated intraocular surgery (e.g., vitreous in anterior chamber, zonular dehiscence)
- History of failed Schlemm's canal procedure (including but not limited to Glaukos iStent, Ellex ABiC, SightSciences Trab360, or New World Medical Kahook Dual Blade)
- Epithelial or fibrous downgrowth

- Aphakia
- Currently implanted anterior chamber IOL
- Retinal laser within 90 days prior to screening
- A need for additional ocular surgery (e.g., cataract surgery) or retinal laser procedure within the 12-month postoperative period
- Proliferative diabetic retinopathy (PDR)
- History of retinal detachment repair with silicone oil or scleral buckling procedure
- Corneal dystrophy (e.g., Fuch's Dystrophy, defined as > 12 confluent endothelial guttae) or corneal opacity
- Previous corneal surgery, including lamellar or penetrating keratoplasty, LASIK or PRK
- Fellow eye best-corrected visual acuity (BCVA) worse than 20/200
- Inability to complete a reliable Humphrey-Zeiss 24-2 SITA Std visual field on the study eye (fixation losses, false positive, and false negative errors should not be greater than 33%)
- Fellow eye visual field mean deviation worse than -18.00 dB
- Exudative age-related macular degeneration (AMD)
- History of intraocular inflammation or infection within 90 days prior to screening
- Use of oral hypotensive medication (e.g., acetazolamide) for glaucoma treatment
- Uncontrolled systemic disease that in the opinion of the Investigator would put the subject's health at risk and/or prevent the subject from completing all study visits
- Unable to suspend or temporarily discontinue use of blood thinners (e.g., warfarin, heparin, aspirin, etc.) in accordance with surgeon's standard instructions
- Pregnant or nursing women; or women of child bearing age not using medically acceptable birth control
- Current participation or participation within the past 30 calendar days in another investigational drug or device clinical trial
- Known or suspected allergy to nickel

3.4 Baseline Inclusion Criteria

- Medicated diurnal IOP ≥ 20 mmHg and ≤ 35 mmHg

3.5 Consent

Participation in the study is voluntary. When it has been established that the patient is eligible for possible enrollment into the study, written informed consent (ICF) will be obtained.

3.6 Enrollment

Patients who sign the informed consent form (ICF) are considered enrolled. Study specific exams should be initiated only after ICF is obtained.

4.0 CLINICAL FOLLOW-UP SCHEDULE

All subjects will be scheduled to return for follow-up examinations at defined intervals through 12 months. **Table 5** shows the schedule of events and procedures at each protocol-required visit.

SCHEDULE OF VISITS

Procedure	**Screening**[1]	**Baseline** (30 days from Scr)	**Surgery** (30 days from BL)	**1D Postop**	**7D Postop** (+/- 2D)	**1M Postop** (30+/- 7D)	**2M Postop** (60+/- 10D)	**3M Postop** (90+/- 14D)	**6M Postop** (183+/- 14D)	**9M Postop** (274+/- 30D)	**12M Postop** (365+/- 45D)
Informed Consent	X										
Medical History *Ophthalmic and Non-Ophthalmic*	X										
Medication Assessment	X	X	X	X	X	X	X	X	X	X	X
Manifest Refraction	X	X			X	X	X	X	X	X	X
BCVA - Snellen	X										
Visual Acuity-Pinhole				X							
BCVA - ETDRS		X			X	X	X	X	X	X	X
Intraocular Pressure *Goldmann Applanation Tonometry*	X			X	X	X	X	X	X	**X**	
Diurnal Intraocular Pressure *Goldmann Applanation Tonometry*		**X**[3]									**X**[3]
Intraocular Pressure *2 to 6 hours after surgery*			X[4]								
Pachymetry CCT	X										X
Gonioscopy	X				X	X	X	X	X	X	X
Slit Lamp Exam	X	X		X	X	X	X	X	X	X	X
Lenticular Opacity Grading	X[5]					X[5]			X[5]		X[5]
Visual Field *Humphrey 24-2 SITA Standard*	X							X	X		X
Fundus Exam/Disc Evaluation	X					X			X		X
Optic Disc Photography		X									X
Subject Questionnaire		X						X			X
Hydrus Implantation			X[6]								
Adverse Event Assessment			X	X	X	X	X	X	X	X	X

[1] At the Screening Visit, all assessments will be performed for both eyes.
[2] At the Baseline Visit, both eyes may be evaluated if eligibility confirmed after all Screening procedures completed.
[3] Daytime-Diurnal IOP measurements will be performed 3 times at 8:00 AM (± 1 hour), 12:00 PM (± 1 hour), and 4:00 PM (± 1 hour).
[4] Single reader method (no masking required) and only one measurement. Goldmann or portable tonometer may be used.
[5] Phakic subjects only.
[6] Subjects who do not receive the microstent during surgery will be followed for safety for 1 month postoperatively or until the device-related adverse event, if applicable, has resolved or is stable.

5.0 STATISTICAL METHODS

5.1 General Data Handling

Descriptive statistics on continuous variables will include mean, standard deviation, median, and range. Confidence intervals will be included for selected endpoints. Categorical variables will be summarized using frequency counts and percentages. A confidence level of 95% will be used for the confidence intervals. Statistical testing will be two-sided with a significance level of 0.05 or one-sided with a significance level of 0.025 unless specify otherwise. Data listings of individual subject data may be provided.

The baseline values are those that are obtained at the closest visit prior to the surgery. The arithmetic difference between the baseline and the postoperative visit are defined as follows:

Change from baseline = postoperative value – baseline value

Percent change from baseline = change from baseline ÷ baseline X 100.

The Safety Population includes all subjects for whom a Hydrus microstent was implanted or implantation was attempted.

5.2 Study Populations

The **Effectiveness Population** will consist of all the subjects who undergo the Hydrus implantation surgery and are not discontinued early from the study due to unrelated reasons such as death or relocation. The primary analyses on the primary and secondary effectiveness endpoints will be based on the **Effectiveness Population**. The reasons for discontinuation will be reported.

Intent to Treat. The ITT population will include all subjects undergoing Hydrus Microstent implantation surgery. For this study the ITT population is the safety population.

Per Protocol. The Per Protocol (PP) population will include all implanted subjects who meet the following criteria:

- Subject meets all protocol eligibility criteria.
- Subject completes the 12-month visit.
- Subject received secondary surgical intervention (SSI) for controlling IOP will be included and treated as non-responder
- Subjects without adverse events that lower IOP such as cyclodialysis cleft.
- Additional criteria, if any, will be established before the data review and database closure.

5.3 Effectiveness Endpoints Analyses

5.3.1 Primary Effectiveness Endpoint

The primary effectiveness outcomes for this study is:

- Proportion of subjects with ≥ 20% decrease in mean diurnal IOP at 12 months while maintaining the same or fewer number of medications as at baseline

The primary analyses of the primary endpoint will be based on the Effectiveness Population. The exact 95% confidence interval of the response rate will be calculated based on binomial distribution.

5.3.2 Secondary Effectiveness Endpoint

The secondary effectiveness endopoint for this study is:

- Mean reduction in diurnal IOP at 12 months.

The change in diurnal IOP from baseline at 12 months will be calculated for each subject, and the mean change in diurnal IOP and the corresponding 95% confidence interval will be calculated.

5.3.3 Other Effectiveness Analyses

The following outcomes will be summarized descriptively at each scheduled visit based on the available data:

- IOP, IOP change, and IOP percent change from baseline
- Number of glaucoma medications and change in the number of glaucoma medications from baseline

5.4 Safety Analyses

Adverse events (AEs) will be classified as intraoperative or postoperative. The AEs will be summarized by counts and percentages. They will also be summarized by severity (mild, moderate, severe) and relationship to the study device and implantation procedure. Additionally, the frequency and percentage of the serious adverse events will be presented. The summaries of the adverse events will be separated by ocular and non-ocular events.

6.0 ADVERSE EVENTS

6.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users or other persons, whether or not related to the microstent or delivery system. Conditions or diseases that are chronic but stable (unchanged) should not be recorded as an AE. Changes in a chronic condition or disease that are consistent with natural disease progression are NOT adverse events and also should not be recorded. Events that occur during the screening period should not be recorded. AEs should be recorded starting with the Operative Visit.

6.1.1 Serious Adverse Events (SAEs)

An AE should be classified as an SAE and reported as such if it meets one or more of the

following criteria:

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted in
  - Life threatening illness or injury,
  - Permanent impairment of a body structure or a body function, or
  - Inpatient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect
- Considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions.
- Hospitalization or prolonged hospitalization required to allow outcome measurement for the study.
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

6.1.2 Sight-Threatening Events

A sight-threatening event should be reported as an SAE. Sight-threatening events include, but are not limited to endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment, or aqueous misdirection.

6.1.3 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application). 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.

6.2 Adverse Event Assessment and Documentation

All subjects who undergo attempted implantation of the Hydrus will be evaluated for adverse events. All adverse events, regardless of severity and whether or not they are ascribed to the Hydrus implant or delivery system, will be recorded using standard medical terminology. All events for the study eye, fellow eye, and non-ocular are to be recorded.

All adverse events will be evaluated beginning with onset, and evaluation will continue until resolution is noted, 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.

All AEs will be characterized by the following criteria:

- Event term
- Severity
- Expectedness
- Relationship to study device or procedure
- 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 more than one distinct adverse event occurs, each event should be recorded separately.

However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

Events occurring secondary to other events should be recorded as sequelae to the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE. Treatment for an adverse event should not be recorded as the adverse event. Instead, the reason for the treatment or procedure should be assessed as the potential adverse event.

6.3 Classification of Adverse Events by Severity

All adverse events should be graded on a three-point scale (mild, moderate, severe) for severity. The 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.

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 (SAE). 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 listed in the protocol.

6.4 Anticipated or Unanticipated Events

All AEs will be evaluated as to whether they are anticipated or unanticipated.

Anticipated: An adverse event is anticipated (i.e., expected) when the nature, severity, or degree of incidence was previously described. Expected adverse events are listed in 8.8.1.

Unanticipated: An adverse event is unanticipated (i.e., unexpected) when the nature, severity, or degree of incidence was not previously described.

6.5 Relationship of the Event to the Device and Procedure

The study investigator will evaluate if the AE is related to the Hydrus device or the Hydrus procedure. Relationship is defined in the following manner:

Not related: Evidence indicates no plausible direct relationship to the study device or procedure, such that:

- A clinically plausible temporal sequence is inconsistent with the onset of the AE and device or procedure; and/or
- A causal relationship is considered biologically implausible; and/or
- The AE can be attributed to concurrent/underlying illness, other drugs, or procedures.

Related: Evidence indicates a reasonable temporal sequence of the event with the study device or procedure exists, or that the association of the event with study device administration is unknown and the event is not reasonably supported by other conditions, such that:

- There is a clinically plausible time sequence between onset of the AE and study device or procedure; and/or
- There is a biologically plausible mechanism for study device or procedure causing or contributing to the AE; and
- The AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures.

Remote: Exposure to the device/procedure and the occurrence of adverse event cannot be reasonably determined to be unrelated to the device or the procedure.

6.6 Ongoing Assessment and Outcome

Adverse events will be assessed at all postop visits until resolution or stabilization occurs. Changes in severity and intervention will be recorded.

The clinical outcome of an AE will be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Stabilization; no possible resolution
- Ongoing (i.e. continuing at time of study discontinuation)
- Death.

After exit from the study, ongoing AEs should be followed until resolution (with or without sequelae), stabilization, or it is determined that there is no possible resolution. Subjects who present or report with a significant, ocular (study eye only) adverse event at the exit visit, should be followed by the physician after exit for AE resolution/stabilization.

6.7 Treatment or Action Taken

- None
- Medical Intervention
- Surgical Intervention (includes device explant)
- Other.

6.8 Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

Serious Adverse Events (SAE) and unanticipated adverse device effects (UADE) must be reported to the study sponsor as soon as possible and no later than 10 working days after the investigator first learns of the event.

For initial reports, investigators should record all case details that can be gathered within the reporting timeframe. Relevant follow-up information should be submitted to the Sponsor as soon as it becomes available and/or upon request. For some events, the sponsor or its designee or the medical monitor may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the subject's subsequent medical course must be submitted to the study sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

The Sponsor will be responsible for informing regulatory authorities and all other IRBs/ECs and Investigators participating in the study of the UADE within 10 working days after notice of the event.

6.8.1 Anticipated Adverse Events

Anticipated AEs associated with glaucoma surgical procedures that might reasonably be expected to occur in this study are listed below. These specific examples of anticipated AEs include, but are not limited to:

Intraoperative Adverse Events

- Choroidal hemorrhage or effusion
- Corneal abrasion
- Corneal edema
- Cyclodialysis cleft
- Hyphema obscuring the surgeon's view
- Inadvertent perforation of the sclera
- Iridodialysis
- Lens / capsular bag damage (crystalline or IOL)
- Microstent malposition
- Significant iris injury or trauma
- Vitreous loss
- Zonular dialysis

Postoperative adverse events include

- Angle closure
- Angle recession
- Anterior chamber cell or flare requiring either an increase in the standard postoperative steroid regimen or re-initiation of steroid use following completion of the standard postoperative steroid regimen.
- Aqueous misdirection
- Atrophy, phthisis
- Best-corrected visual acuity loss of 2 lines (10 letters) or more compared to baseline on the ETDRS chart measured before or at 1-month postoperative
- Best-corrected visual acuity loss of 2 lines (10 letters) or more compared to baseline on the ETDRS chart measured after 1-month postoperative
- Blebitis
- Choroidal detachment
- Choroidal hemorrhage or effusion (detachment with at least a partially hemorrhagic component that obstructs or causes pain, including both peripheral and "kissing" choroidal detachments) lasting 30 days or less
- Choroidal hemorrhage or effusion (detachment with at least a partially hemorrhagic component that obstructs or causes pain, including both peripheral and "kissing" choroidal detachments) lasting longer than 30 days
- Chronic anterior uveitis defined as inflammation of grade 1+ or worse persisting for more than 90 days postoperatively or that recurs less than 90 days after discontinuing standard medication regimen
- Chronic pain in the study eye onset ^{3} 3-months postoperative
- Corneal decompensation

- Corneal edema persisting > 30 days (mild to moderate) or severe corneal edema ≥ 1 day.
- Corneal opacification
- Descemet's membrane detachment
- Device migration (dislodgement or movement)
- Device obstruction
- Elevated mean IOP ≥ 10 mmHg than the qualifying baseline mean IOP onset before or at 1-month postoperative
- Elevated mean IOP ≥ 10 mmHg than the qualifying baseline mean IOP onset after 1-month postoperative
- Endophthalmitis
- Flat anterior chamber with lens/cornea touch or shallow anterior chamber with peripheral iridocorneal apposition
- Hyphema ≥ 2 mm in height (layered) at any time
- Hyphema present or arising > 30 days postoperative
- Hypotony (defined as IOP < 6 mmHg) onset before 1-month postoperative
- Hypotony (defined as IOP < 6 mmHg) onset at or after 1-month postoperative
- Implant corneal touch
- Implant-iris touch associated with intraocular inflammation, pigment dispersion, or other sequelae
- Inadvertent bleb
- Increase in vertical C/D ratio of ≥ 0.3 units from screening on fundus examination
- Iris prolapse/wound incarceration
- Maculopathy including hypotonic maculopathy
- Persistent diplopia
- Pupil block
- Retinal complications (e.g., flap tears, retinal break, retinal detachment, age related macular degeneration, diabetic retinopathy, macular edema, epiretinal membrane, central serous retinopathy, or proliferative vitreoretinopathy)
- Scleral ectasia
- Surgical re-intervention in the study eye (other than paracentesis to relieve pressure within the 1 week visit)
- Toxic anterior segment syndrome (TASS)
- Vitreous haze
- Vitreous hemorrhage
- Vitritis
- Worsening of 2-points (from screening) to "severe" on the slit lamp examination findings (other than cells and flare) onset at or after 3-months postoperative not associated with a pre-existing condition
- Worsening of lens opacities (defined as a 2.0 or more score change on at least one category of the LOCS III grading system, at 2 or more consecutive visits)
- Worsening of visual field (mean deviation worsening by 3.0 dB or more, confirmed by 2 repeat measurements)
- Wound dehiscence (persistent aqueous leak or fistula formation)

For any adverse event that may be due to incorrect device positioning (i.e. vitreous hemorrhage, hyphema, hypotony), gonioscopy should be performed to assess the device position. If the position cannot be adequately evaluated by gonioscopy, ultrasound biomicroscopy (UBM) should be performed.

For slit lamp examination, gonioscopy and fundus findings for which there is no grading scale, any finding considered by the study investigator to be marked or severe, i.e., clinically significant, should be recorded as an Adverse Event.

7.0 DEFINITIONS

Device Obstruction

No obstruction: Tissue located around the inlet (portion of device in anterior chamber), however the flow path from the anterior chamber into Schlemm's canal is not obstructed.

Device obstruction: Inlet (portion of device in anterior chamber) is filled with tissue resulting in an obstructed flow path from the anterior chamber into Schlemm's canal.

Endophthalmitis: Diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause; if known; record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms on AE pages of the CRF.

Peripheral anterior synechia (PAS): Iris adhesions that cross the scleral spur and adhere to the peripheral cornea, not including iris processes.

Malposition: Gonioscopic evidence that all windows of the microstent and/or distal end are not in Schlemm's canal.

Uveitis: Inflammation in the uveal tract (iris, ciliary body, and choroid), either primary or secondary to keratitis or systemic diseases. Includes iritis (presence of inflammatory cells in the anterior chamber; aqueous flare alone is not considered to constitute iritis) and iridocyclitis (presence of inflammatory cells in both the aqueous and vitreous).

Vitreous Haze: A worsening of inflammation by 2 grades or a finding of Grade 3 (optic nerve head is visible but the borders are blurry and cannot see vessels) or Grade 4 (optic nerve head is obscured) on the grading scale provided in Appendix 2.

Vitreous Hemorrhage: A worsening of density by 2 grades or a finding of Grade 3 (Red reflex is visible but no central retinal detail is seen posterior to the equator by ophthalmoscopy) or Grade 4 (No red reflex on ophthalmoscopy) on the grading scale provided in Appendix 2.

Vitritis: Presence of active inflammation in the vitreous, as demonstrated by the presence of inflammatory cells (trace or greater).

- The presence of inflammation involving only the anterior vitreous will not be considered to constitute vitritis because it may result from iridocyclitis (see above).
- Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.
- The presence of vitreous flare alone in the absence of active inflammatory cells will not be considered to constitute vitritis.

Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.