

PROTOCOL NCT01539239

THE SAFETY AND EFFECTIVENESS OF THE HYDRUS AQUEOUS IMPLANT FOR LOWERING INTRAOCULAR PRESSURE IN GLAUCOMA PATIENTS UNDERGOING CATARACT SURGERY, A PROSPECTIVE, MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL

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1.0 DEVICE DESCRIPTION

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

The microstent (**Figure 1**) is composed of nitinol, a metal alloy of nickel (Ni) and titanium (Ti). Nitinol has been used extensively in a variety of implantable 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. Its flexibility and small size allows delivery of the microstent through tortuous, restrictive passages with minimal force. The implant is laser cut from nitinol tubing 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 microstent is approximately 8mm in overall length with major and minor axes of 292 μ m and 185 μ m, respectively. 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.

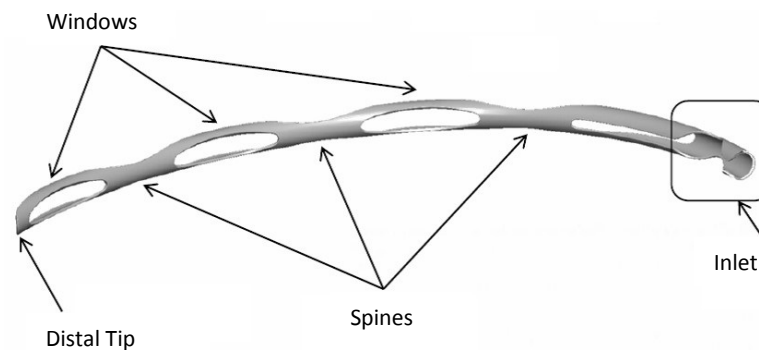


FIGURE 1: HYDRUS IMPLANT

The microstent is implanted into the eye using a hand-held delivery system (**Figure 2**) that provides for manual delivery of the implant 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 delivery system 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.

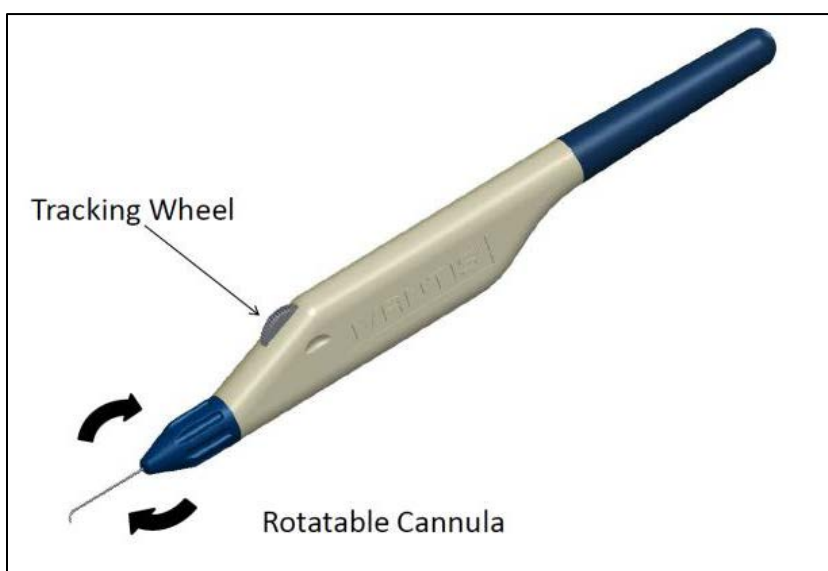


FIGURE 2: HYDRUS DELIVERY SYSTEM

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 ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the correction of mild to moderate POAG. These alternatives include:

- Non-surgical treatment, such as IOP-lowering medications (topical eye drops or systemic IOP lowering drugs)
- Laser treatment
- Other incisional glaucoma surgery

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

3.0 MARKETING HISTORY

The Hydrus Microstent is currently approved for commercial distribution in the European Union, Canada, Australia, New Zealand, Costa Rica and Columbia.

The Hydrus Microstent has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

4.0 SUMMARY OF NONCLINICAL STUDIES

A. BIOCOMPATIBILITY TESTING

Biocompatibility testing was performed on the Hydrus implant or representative samples of the finished device (**Table 1A**) and on the patient-contacting components of the Hydrus delivery system (**Table 1B**). The biocompatibility testing was performed in accordance with *ISO 10993-1 - Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process* and relevant related sub-standards, including:

- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- Part 5: Tests for *in vitro* cytotoxicity
- Part 6: Tests for local effects after implantation
- Part 10: Tests for irritation and skin sensitization
- Part 11: Tests for systemic toxicity

All biocompatibility testing was conducted in accordance with the provisions of *21 CFR 58, Good Laboratory Practice for Nonclinical Laboratory Studies*.

TABLE 1A: BIOCOMPATIBILITY TESTING OF THE HYDRUS IMPLANT

Test	Test Method	Results
Cytotoxicity	MEM Elution ISO 10993-5	Non-cytotoxic
Cytotoxicity	Agarose Overlay (Direct Contact) ISO 10993-5	Non-cytotoxic
Cytotoxicity	Cell Growth Inhibition Assay ISO 10993-5	Negative
Sensitization	Guinea Pig Maximization ISO 10993-10	Non-sensitizer
Intracutaneous Reactivity	Rabbit Intracutaneous Reactivity ISO 10993-10	Non-irritant
Acute Systemic Toxicity	Mouse USP Systemic Injection ISO 10993-11	Non-toxic
Material Mediated Pyrogenicity	Rabbit Pyrogen ISO 10993-11:2006	Non-pyrogenic
Subacute Intraperitoneal Toxicity	Mouse 14-Day Intraperitoneal Injection ISO 10993-11	Non-toxic
Subchronic Intravenous Toxicity	Mouse 14-Day Intravenous Injection ISO 10993-11	Non-toxic
Mutagenicity	Ames Reverse Mutation ISO10993-3	Non-mutagenic
Mutagenicity	Mouse Micronucleus ISO10993-3:2003	Non-genotoxic
Mutagenicity	Mouse Lymphoma ISO10993-3:2003	Non-mutagenic
Intramuscular Implantation	Rabbit Muscle Implantation (13 weeks) ISO 10993-6:2007	No different than control
Chronic Toxicity	6-Month Ocular Implantation Testing in Rabbits	No different than control

TABLE 1B: BIOCOMPATIBILITY TESTING OF THE HYDRUS DELIVERY SYSTEM

Test	Test Method	Results
Cytotoxicity	MEM Elution ISO 10993-5	Non-cytotoxic
Sensitization	Guinea Pig Maximization ISO 10993-10	Non-sensitizer
Intraocular Irritation	Intraocular Exposure in Rabbits	Non-irritant
Intracutaneous Irritation	Rabbit Intracutaneous Reactivity ISO 10993-10	Non-irritant
Acute Systemic Toxicity	Mouse USP Systemic Injection ISO 10993-11	Non-toxic
Material Mediated Pyrogenicity	Rabbit Pyrogen ISO 10993-11	Non-pyrogenic

B. PHYSICOCHEMICAL TESTING

Physicochemical testing was conducted to physically characterize and verify the stability of the microstent throughout the potential implant life span.

Physicochemical testing (**Table 2**) was conducted on the Hydrus implant (or representative samples of the finished device) in accordance with *ANSI Z80.27 - Ophthalmics - Implantable Glaucoma Devices* and *FDA Guidance Document - Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices (December 15, 2015)*.

TABLE 2: PHYSICOCHEMICAL TESTING OF THE HYDRUS IMPLANT

Test	Purpose	Results
Corrosion Resistance	Determine susceptibility of microstent to galvanic corrosion per ASTM F 2129-08	Microstent is considered corrosion resistant
Exhaustive Extraction	Determine identity and amount of extractable substances	No extractable substances at levels that would affect the human eye
Leachables	Determine identity and amount of saline leachables	No leachable substances at levels that would affect the human eye
Nickel Elution	Quantify amount of nickel ion released from microstent	Risk of adverse effects resulting from nickel leaching is negligible
Hydrolytic Stability	Demonstrate 5 year accelerated hydrolytic stability of the microstent <i>in situ</i>	Microstent is hydrolytically stable for 5 years; no detectable adverse effect on surface characteristics of finished microstents
Insoluble Organics	Evaluate microstent for evidence of inorganic compounds on the finished device at the end of the manufacturing process	No significant levels of insoluble organics detected

C. PHYSICAL AND MECHANICAL TESTING

The Hydrus implant and delivery system were subjected to physical and mechanical testing in accordance with ANSI Z80.27 (**Table 3**).

TABLE 3: PHYSICAL AND MECHANICAL TESTING OF THE HYDRUS MICROSTENT

Test	Purpose	Results
Material Properties Nitinol (NiTi) Alloy	Verify nitinol base material satisfies composition and mechanical characteristics for surgical implants per ASTM F2063-12	Each lot of microstents is provided with a Certificate of Conformance to ASTM F2063-12
Austinetic Finish Transition Temperature (A_f)	Verify A_f transition temperature of microstent following heat-set operation satisfies specification of $16 \pm 3^\circ \text{C}$	Each lot of microstents is tested for A_f transition temperature by differential scanning calorimetry testing per ASTM F2004
Dimensions	Verify overall dimensions are within specifications	Each lot of microstents is inspected for nominal length, wall thickness and radius of curvature
Edge and Surface Quality	Verify edges and surface of microstent are smooth, free of cracks, protrusion, pits, dings, inclusions and stringers	Each lot of microstents is subjected to surface/edge inspection by light microscopy and SEM
Structural Integrity	Verify microstent satisfies mechanical strength requirements per ANSI Z80.27-14	Tensile force testing shows force at breakage $> 0.5 \text{ N}$, satisfying requirements of ANSI Z80.27-2014
Outflow Facility	Verify microstent is able to increase outflow of aqueous humor sufficient to lower IOP in bench test model	Benchtop testing demonstrates significant increase in outflow facility in cadaver eyes
Magnetic Resonance Imaging Compatibility	Evaluate the compatibility of the microstent with current standard magnetic resonance imaging techniques	Microstent shown to be “MR-conditional” and labeled appropriately per ASTM F2503-13
Delivery System Performance	Verify delivery system consistently satisfies performance requirements for microstent delivery	Performance testing demonstrates that the microstent is consistently delivered under conditions of <i>in vitro</i> bench testing and simulated <i>in vivo</i> use in cornea rim tissue

D. STERILIZATION, PACKAGE INTEGRITY, SHELF LIFE, AND TRANSPORT STABILITY

The Hydrus Microstent is supplied with the implant pre-loaded in the handheld delivery system. The device is sealed in sterile-barrier (Tyvek®) packaging and packaged in a chipboard shelf box.

The packaged device is sterilized by exposure to gamma radiation. Microbiological studies have been conducted to demonstrate that the packaged device satisfies domestic and international requirements to be labeled 'STERILE' with a Sterility Assurance Level (SAL) of 10^{-6} . The sterilization cycle was validated in accordance with the provisions of *ISO 11137-1:2006 - Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices* and *ISO 11137-2:2012 - Sterilization of health care products – Radiation - Part 2: Establishing the sterilization dose*. The methodology used was that applicable to substantiating 25 kGy as a minimum sterilization dose (Method VD_{max}25). Successful completion of the sterilization validation qualifies dose monitoring as a means for routine lot release of the device.

Sterilization, packaging, shipping, and shelf life studies were conducted to verify that the packaging for the device maintains a sterile barrier and that the device performance meets product specifications through the labeled shelf life. The results of the sterilization, packaging, shelf life and transport stability studies are summarized in **Table 4**.

TABLE 4: STERILIZATION, PACKAGING, TRANSPORTATION AND SHELF LIFE TESTING

Test	Purpose	Results
Gamma Irradiation Sterilization Validation	Demonstrate device is 'STERILE' to an SAL of 10^{-6}	Satisfies requirements of ISO 11137-1 to be labeled 'Sterile' with an Sal of 10^{-6}
Bioburden	Establish upper limit for product bioburden to establish sterility of (≤ 200 CFU/Device)	Bioburden testing shows results ≤ 200 CFU/Device
Bacterial Endotoxin	Verify bacterial endotoxin levels satisfy FDA Guidance for single-use ophthalmic devices (≤ 0.2 EU/Device)	Bacterial endotoxin testing shows results < 0.2 EU/Device
Package Evaluation – Bubble Leak	Verify package seal integrity	No bubble leak per ASTM F2096
Package Evaluation – Seal Peel Test	Verify package seal integrity	Package seal peel strength ≥ 1.0 Lbf
Transport Stability	Verify package and device stability after transportation challenges	Packaging and device satisfy specifications after transport challenges per ASTM D4169, distribution cycle 13
Shelf Life Stability	Verify sterile-barrier packaging and device satisfy specifications through labeled expiration date	Sterile-barrier packaging and device satisfy specifications after aging to the labeled expiration date

5.0 STUDY METHODS

A. SELECTION OF PATIENTS

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

B. GLAUCOMA DIAGNOSIS

Glaucoma is a progressive optic neuropathy that results in characteristic optic disc and visual field changes. To qualify for the study, all subjects must have optic disc changes characteristic of glaucoma.

C. INCLUSION CRITERIA

Subjects must meet the following inclusion criteria to be eligible for the study eye:

- Male and female patients, at least 45 years of age
- An operable age-related cataract with BCVA of 20/40 or worse, eligible for phacoemulsification; if BCVA is better than 20/40, testing with a BAT meter on a medium setting must result in BCVA 20/40 or worse
- A diagnosis of POAG treated with 1 to 4 hypotensive medications
- Optic nerve appearance characteristic of glaucoma
- Medicated IOP \leq 31 mmHg
- Diurnal IOP \geq 22 mmHg and \leq 34 mmHg after wash out of ocular hypotensive medications
- IOP increase \geq 3 mmHg after wash out of ocular hypotensive medications
- Visual field examination using Humphrey 24-2 SITA standard, meeting protocol specified minimum criteria for glaucoma defined as:
 1. **Mild:** visual field loss on Humphrey visual field testing, with mean deviation (MD) between 0 and -6dB; fewer than 25% of points depressed below the 5% level and fewer than 15% of points depressed below the 1% level on pattern deviation plot; and no point within central 5° with sensitivity <15dB.
 2. **Moderate:** visual field loss on Humphrey visual field testing, with mean deviation worse than -6dB but no worse than -12dB; fewer than 50% of points depressed below the 5% level, and fewer than 25% of points depressed below the 1% level on pattern deviation plot; no points within central 5° with sensitivity of \leq 0dB; and only one hemifield containing a point with sensitivity <15dB within 5° of fixation.

- In subjects where the VF exam is not confirmatory for glaucomatous defect, retinal nerve fiber layer optical scanning laser imaging supporting ophthalmoscopy findings shall be performed
- Shaffer grade \geq III in all four quadrants
- Cup:disc (c:d) ratio \leq 0.8
- Absence of peripheral anterior synechiae (PAS), rubeosis or other angle abnormalities that could impair placement of the implant
- Subject is able and willing to attend scheduled follow-up exams for 2 years post-operatively (and up to 5 years postoperatively as part of a post-approval study)
- Subject understands and signs the informed consent

D. INTRAOPERATIVE ELIGIBILITY CRITERIA

Individuals who meet the following intraoperative eligibility criteria in the study eye will be randomized into the treatment or control arms of this study.

Subjects must have:

- An intact and centered capsulorrhexis
- An intact posterior capsular bag
- A well-centered monofocal IOL placed in the capsular bag
- A clear view of an open angle and visualization of the angle with direct gonioscopy following intracameral instillation of a miotic agent

Subjects must not have:

- Evidence of zonular dehiscence/rupture
- Intraoperative floppy iris syndrome

E. 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.

- Closed angle forms of glaucoma
- Congenital or developmental glaucoma
- Secondary glaucoma (such as neovascular, uveitic, pseudoexfoliative, pigmentary, lens-induced, steroid-induced, trauma induced, or glaucoma associated with increased episcleral venous pressure).
- Use of more than 4 ocular hypotensive medications (combination medications count as two medications).
- Previous argon laser trabeculoplasty, trabeculectomy, tube shunts, or any other prior filtration or cilioablative surgery.

- Prior surgery for an ab-interno or ab-externo device implanted in or through the Schlemm's Canal.
- Inability to complete a reliable 24-2 SITA Standard Humphrey visual field on the study eye at screening (fixation losses, false positive errors and false negative errors should not be greater than 33%).
- Use of oral hypotensive medication for glaucoma for treatment of the fellow eye.
- Subjects with advanced glaucoma or any subject who presents with an unacceptable risk to the subject of a washout of ocular hypotensive medications.
- Best corrected visual acuity worse than 20/80 in the fellow eye.
- A 24-2 SITA Standard Humphrey visual field mean deviation (MD) of worse than -12dB in the fellow eye.
- Central corneal thickness > 620 microns and < 480 microns.
- Proliferative diabetic retinopathy.
- Previous surgery for retinal detachment.
- Previous corneal surgery or clinically significant corneal dystrophy, e.g., Fuch's dystrophy (>12 confluent guttae)
- Unclear ocular media preventing visualization of the fundus or anterior chamber angle.
- Degenerative visual disorders such as wet age-related macular degeneration.
- Clinically significant ocular pathology, other than cataract and glaucoma.
- Clinically significant ocular inflammation or infection within 6 months prior to screening.
- Presence of extensive iris processes that obscure visualization of the trabecular meshwork.
- Unable to discontinue use of blood thinners in accordance with surgeon's standard postoperative instructions.
- Known or suspected elevated episcleral venous pressure due to Sturge Weber, nanophthalmos, orbital congestive disease.
- 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.
- Current participation or participation in another investigational drug or device clinical trial (which includes the fellow eye) within the past 30 calendar days.
- Pregnant or nursing women; or women of child bearing age not using medically acceptable contraceptives.

F. CONSENT

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

G. ENROLLMENT

Patients who sign the informed consent form (ICF) are considered enrolled. Only after ICF is obtained should study specific exams and wash out be initiated.

H. WASH OUT

After the subject has successfully completed the preoperative screening exam, the subject will be instructed to discontinue ocular hypotensive medications in the designated treatment eye for the appropriate washout period.

6.0 CLINICAL FOLLOW-UP SCHEDULE

All subjects will be scheduled to return for follow-up examinations at defined intervals through 24 months. **Table 5** shows the schedule of events and procedures at each protocol-required visit.

TABLE 5: SCHEDULE OF EVENTS AND PROCEDURES

Procedure	Screening (Both Eyes) (w/in 30d of washout start)	Baseline (w/in 13d of minimum washout)	Surgery (w/in 14d of minimum washout)	1D Postop	7D Postop (±2d)	1M Postop (±7d)	3M Postop (±14d)	6M Postop (±21d)	12M Postop (-28d/ +42d)	18M Postop (±28d)	24M Postop (-28d/ +42d)	3Y, 4Y & 5Y Postop (±84d)
Ophthalmic and medical history	X											
Ocular Medication Status	X	X	X	X	X	X	X	X	X	X	X	X ⁵
Glaucoma Medication Status	X	X	X	X	X	X	X	X	X	X	X	X ⁵
Manifest Refraction	X	X			X	X	X	X	X	X	X	
BCVA	X (Snellen)	X (ETDRS)		X (pinhole) (Snellen)	X (ETDRS)	X (ETDRS)	X (ETDRS)	X (ETDRS)	X (ETDRS)	X (ETDRS)	X (ETDRS)	X (Snellen)
IOP (Goldmann Applanation Tonometry)	X			X	X	X	X	X	X ²	X	X ²	X ⁶
Washed Out Diurnal IOP (Goldmann Applanation Tonometry)		X ¹							X ¹		X ¹	
Pachymetry CCT	X							X	X		X	X
Gonioscopy	X				X	X	X	X	X	X	X	X
Slit Lamp Exam	X	X		X	X	X	X	X	X	X	X	X
Visual Field (Humphrey 24-2 SITA-Std)	X							X	X		X	X
Fundus Exam/Disc evaluation	X					X		X	X		X	X
Specular Microscopy	X						X	X ⁷	X ⁷	X ⁷	X ⁷	X ⁷
Nerve Fiber Layer Imaging	X ³											
Ocular Symptom Questionnaire		X							X		X	
Adverse Event Assessment		X ⁴	X	X	X	X	X	X	X	X	X	X ⁸

¹Washed out diurnal IOP measurements will be performed after subject has washed out of any ocular hypotensive medications. All diurnal IOP measurement must be done PRIOR to the Gonioscopy, Fundus Exam and contact Pachymetry. An additional visit may be necessary to perform the diurnal IOP measurements.

²Only required for those subjects taking ocular hypotensive medications at the time of this visit.

³Only required for those subjects whose VF testing was not confirmatory for glaucomatous defect per the protocol defined criteria.

⁴Only adverse events associated with the ocular medication wash out.

⁵Study eye only for ocular medications other than hypotensive medications.

⁶Single operator tonometry may be conducted at 3, 4 and 5 year visits.

⁷Includes specular microscopy of the fellow eye for the central region only

⁸Report all SAEs and only study eye ocular AEs.

7.0 STATISTICAL ANALYSIS PLAN - STUDY ENDPOINTS

A. THE PRIMARY EFFECTIVENESS ENDPOINT FOR THIS STUDY

Percentage of subjects with a reduction of at least 20% (i.e., $\geq 20\%$) in mean diurnal IOP from baseline in the study eye at 24 months following medication washout. These subjects were defined as “IOP responders.”

Subjects were defined as non-responders if they did not achieve the primary effectiveness endpoint, they were missing 24-month IOP assessment outcomes, if ocular hypotensive medications were not washed out at the 24-month visit, if they underwent an IOP-affecting secondary surgical procedure (i.e., iridotomy, iridectomy, trabeculectomy, glaucoma shunt implantation, argon laser trabeculoplasty, selective laser trabeculoplasty), or other surgery that would affect IOP.

B. THE SECONDARY EFFECTIVENESS ENDPOINT FOR THE STUDY

The mean diurnal unmedicated IOP change from baseline at 24 months was compared between the Hydrus group and control group.

Each endpoint requires a comparison between the Hydrus and control groups. The primary effectiveness analysis will be performed using the Intent to Treat (ITT) population, consisting of all randomized subjects grouped according to their randomization assignment.

With regard to safety, anticipated and unanticipated AEs will be reported for all subjects randomized in the study. Best corrected visual acuity (BCVA), central corneal pachymetry, slit lamp and fundus exams, gonioscopy and central corneal endothelial cell density (ECD) will also be used to assess safety.

C. ACCOUNTABILITY OF PMA COHORT

Subjects will be analyzed according to 3 separate population cohorts:

ITT Population – all subjects randomized and grouped according to their randomization assignment (as randomized). The ITT will be used for the analyses of the primary and secondary effectiveness endpoints.

Per Protocol Population – ITT subjects that met the following conditions:

- Met all protocol eligibility criteria
- Had treatment consistent with randomization schedule
- Completed the 24-month medication washout without secondary surgical intervention to control IOP or additional procedures that could affect IOP (such as cyclodialysis cleft)

- Had preoperative visual field mean deviation (MD) of <0
- Without major protocol deviation established before the data review and database closure

Safety Population – all subjects who were randomized and treated. Subjects in the Hydrus group will be grouped according to whether the implantation procedure was attempted (as treated) and includes those subjects for whom implantation was not successful.

8.0 **ADVERSE EVENTS**

A. **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 investigational medical device. Conditions or diseases that are chronic but stable (unchanged) should not be recorded on AE pages of the CRF. Changes in a chronic condition or disease that are consistent with natural disease progression are NOT adverse events and also should not be recorded on the AE pages of the CRF.

B. **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.

C. SIGHT-THREATENING EVENTS

An event considered sight-threatening, e.g., endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment, aqueous misdirection, etc., should be reported as an SAE if it meets one or more of the following criteria:

- Resulted in permanent loss of sight and did not require medical or surgical intervention.
- Required surgical intervention to prevent permanent loss of sight.
- In the opinion of the investigator it may require medical intervention to prevent permanent loss of sight.

D. 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.

E. ADVERSE EVENT ASSESSMENT AND DOCUMENTATION

All subjects who have been exposed to the study treatment will be evaluated for adverse events. All adverse events, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents and CRF using standard medical terminology. During the post 24 month period (annual visits at 3, 4 and 5 years), AEs will be reported in accordance with **Table 5**.

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 on the concomitant medication case report form.

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 on the CRF 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).

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.

F. 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 Section VIII.L.

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

H. 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
- 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.

I. OUTCOME

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

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

J. TREATMENT OR ACTION TAKEN

- None
- Medical Intervention
- Surgical Intervention (includes device explantation)
- Other

K. 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.

L. ANTICIPATED ADVERSE EVENTS

Anticipated AEs associated with glaucoma and/or cataract 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

Complications of cataract surgery

- Anterior capsule tear
- Posterior capsular rupture
- Vitreous in the anterior chamber
- Choroidal detachment

Other complications

- Hyphema obscuring the surgeon's view
- 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 1 month)
- Choroidal detachment
- Significant iris injury or trauma
- Corneal abrasion
- Corneal edema
- Zonular dialysis
- Cyclodialysis
- Cyclodialysis cleft
- Iridodialysis
- Vitreous loss not associated with the cataract procedure
- Inadvertent perforation of the sclera

Postoperative adverse events include

- Angle recession
- Chronic pain in the study eye ≥ 3 months postoperative
- Flat anterior chamber with lens/cornea touch or shallow anterior chamber with peripheral iridocorneal apposition

- Best-corrected visual acuity loss of 2 lines (10 letters) or more on the ETDRS chart measured at or after 3 months postoperative
- Hypotony (defined as IOP < 6 mmHg) at or after 1 month postoperative
- Maculopathy including hypotonic maculopathy
- Descemet's membrane detachment
- Device migration (dislodgement or movement)
- Device obstruction, partial or complete
- Implant corneal touch
- Inadvertent bleb
- Scleral ectasia
- Wound dehiscence (persistent aqueous leak or fistula formation)
- Anterior chamber cell and 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
- Peripheral anterior synechia (PAS) with device obstruction
- Peripheral anterior synechia (PAS) without device obstruction
- Endophthalmitis
- Layered hyphema
- Circulating blood in the AC and/or vitreous cavity
- Corneal opacification
- Corneal decompensation
- Corneal edema persisting > 1 month (mild to moderate) or severe corneal edema ≥ 1 day
- Retinal complications (flap tears, retinal detachment, or proliferative vitreoretinopathy)
- Elevated mean IOP ≥ 10 mmHg than the qualifying baseline mean IOP > 1 month postoperative
- Surgical re-intervention in the study eye (other than paracentesis to relieve pressure prior to 1 week postoperative)
- Atrophy, phthisis
- Iris prolapse/wound incarceration
- Significant foreign body sensation at or after 3 months postoperative
- Increase in C/D ratio of ≥ 0.3 units on fundus examination
- Worsening of visual field (mean deviation worsening by 2.5 dB or more, confirmed by 2 repeat measurements)
- 2-point worsening to 4+ anterior chamber cells or flare at or after 3 months postoperative, not associated with a pre-existing condition

- 2-point worsening to severe on the slit lamp or fundus examination findings (other than cells and flare) at or after 3 months postoperative not associated with a pre-existing condition
- 2-point worsening of ocular symptoms to severe or very severe at or after 3 months postoperative not associated with a pre-existing condition

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, an ultrasound biomicroscope (UBM) should be performed.

For slit lamp 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.

9.0 **DEFINITIONS**

Iritis: Presence of inflammatory cells in the anterior chamber. The presence of aqueous flare alone is not considered to constitute iritis.

Iridocyclitis: Presence of inflammatory cells in both the aqueous and vitreous.

Uveitis: Inflammation in the uveal tract (iris, ciliary body, and choroid), either primary or secondary to keratitis or systemic diseases.

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.

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.

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.

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.