A PROSPECTIVE, MULTICENTER, RANDOMIZED COMPARISON OF THE HYDRUS™ TO THE ISTENT ™ FOR LOWERING INTRAOCULAR PRESSURE IN PRIMARY OPEN ANGLE GLAUCOMA (THE HYDRUS V TRIAL)

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PROTOCOL #: NCT02023242

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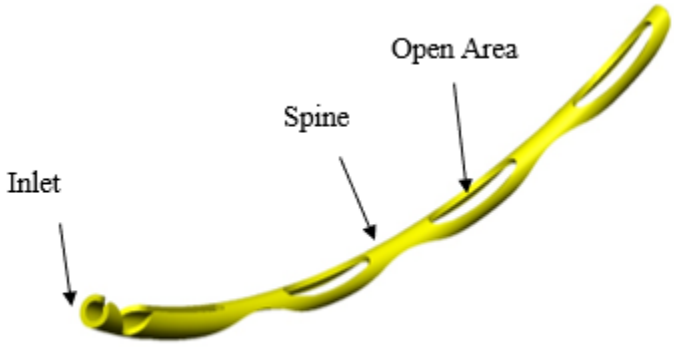
1.0 DEVICE DESCRIPTION

The Hydrus Aqueous Implant is a crescent-shaped implantable device pre-loaded onto a hand-held delivery system. The Implant is delivered into Schlemm's canal by inserting the cannula of the delivery system through the trabecular meshwork and advancing the implant through the cannula. Once the implant is in position, the central core wire of the delivery system is retracted, allowing complete detachment of the Hydrus Aqueous Implant. Upon implantation, the crescent-shaped device provides a support structure, serving to dilate and restore the natural aqueous outflow pathway through Schlemm's canal, leading to a reduction of intraocular pressure.

The Hydrus Aqueous Implant is composed of nitinol, a metal alloy composed of nearly equal parts 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. Its flexibility and small size allow delivery of the Hydrus through torturous, restrictive passages with minimal force. The Hydrus Aqueous Implant is illustrated in Figure 1, on the following page.

Figure 1: The Hydrus™ Aqueous Implant



2.0 STUDY OBJECTIVE AND DESIGN

The objective of this clinical trial is to compare the effectiveness of one *Hydrus* to two iStents for lowering intraocular pressure (IOP) in patients with mild-to-moderate primary open angle glaucoma (POAG), pseudoexfoliative glaucoma (PXG), or pigmentary glaucoma (PG).

This study is a prospective, multicenter, single masked, randomized, clinical trial in which a total of 160 subjects (80 per study arm) will be treated with either one Hydrus or two iStents for treatment of POAG, PXG, or PG in subjects with a phakic lens. The study will be conducted according the Declaration of Helsinki. All study subjects must sign the Informed Consent prior to initiating participation in the study.

Key inclusion criteria for this study are a diagnosis of POAG, PXG, or PG based on optic nerve neuropathy, an open angle, and elevated IOP of 23-39 mmHg in the absence of hypotensive medications. In order to address the confounding effect of medications on the IOP-reducing ability of the devices, a "wash-out" of all glaucoma medications will be conducted, and a 'diurnal' methodology will be utilized to determine the subject's eligibility. The duration of wash-out will be determined by the specific medication(s) used.

Upon successfully meeting the study inclusion/exclusion criteria, subjects will be scheduled for surgery. Randomization will take place on the day of surgery just prior to treatment. Randomization sequence will be based on pre-determined computer-generated lists.

Follow up will be continued for 2 years post-surgery, and will include assessments of the subject's IOP, ocular health, and visual acuity status. Visits will be conducted at 1, 7, 30, 180, 365, 540, and 730 days.

In the event a study subject does not respond to device therapy, hypotensive glaucoma medications may be prescribed in order to reduce IOP to a safe level, as determined by the judgment of the attending physician. Medications of the same type used prior to wash out will be re-started in this event. Re-medication will not be considered an adverse event, but will be monitored. Neither the Hydrus nor the iStent devices preclude the ability to later perform filtration surgery, in the event medications do not lower pressure adequately and more invasive therapy is required.

3.0 STUDY ENDPOINTS

The primary effectiveness endpoint for this study is the proportion subjects with IOP ≤19 mmHg *and* without the use of ocular hypotensive medications at 12 months, as measured by Goldmann tonometry.

Secondary effectiveness endpoints include:

- The proportion of subjects who are are not using ocular hypotensive medications at 12 and 24 months, as measured by Goldmann tonometry
- Mean medication use at 12 and 24 months
- The proportion subjects with IOP ≤19 mmHg *and* without the use of ocular hypotensive medications at 24 months, as measured by Goldmann tonometry

Safety endpoints include:

- Frequency of loss in BCVA of 2 lines or more at 12 and 24 months,
- Slit lamp and fundus examination findings at 12 and 24 months,
- Frequency of complications and adverse events at all follow up periods.

4.0 STATISTICAL METHODS

4.1 Study Hypothesis

A 20% or greater reduction in the proportion of subjects requiring ocular hypotensive medications to reach a target IOP of 19 mmHg or less is a clinically significant treatment effect.

4.2 Sample Size

The study size is based on the primary endpoint.

4.3 Safety Analysis

Safety data (adverse events, visual acuity measurements, perimetry, and ocular health findings based on slit lamp and fundus examinations) will be evaluated using descriptive

statistics. Frequency tabulations of safety outcomes will be performed for 1, 3, 6, 12, 18 and 24-month follow up periods. Safety analysis cohorts will be grouped by actual treatment. The study is not designed to detect differences in safety outcomes.

5.0 STUDY POPULATION

5.1 Inclusion Criteria

Subjects who meet the following inclusion and exclusion criteria will be eligible for enrollment in this study. Ocular criteria relates to the study eye only.

- Male and female patients from 45 to 84 years of age.
- A diagnosis of primary open angle glaucoma (POAG), pseudoexfoliative glaucoma (PXG), or pigmentary glaucoma (PG).
- A phakic patient with BCVA of 20/30 or better.
- A pseudophakic patient who has had cataract surgery >6 months from the time of study enrollment.
- Subject is on ≥2 glaucoma medications at Screening.
- Normal angle anatomy by gonioscopy with a Shaffer angle grade of ≥III in all four quadrants.
- Optic nerve pathology characteristic of glaucoma described by at least one of the following:
  A) Thinning, narrowing, or notching of the optic disc rim.
  B) Diffuse optic disc cupping or asymmetric cupping.
  C) Diffuse or localized peripapillary retinal nerve fiber layer loss.
- After glaucoma medication wash-out, a mean diurnal IOP of 23-39 mmHg by Goldmann applanation tonometry.
- The subject can safely tolerate periodic wash out of glaucoma medications.
- The subject is able to understand the requirements of the study and is willing to follow study instructions, provide written informed consent, and agree to comply with all study requirements.

5.2 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.

- Other secondary glaucoma (such as neovascular, uveitic, traumatic, steroid induced, lens induced, or glaucoma associated with increased episcleral venous pressure).
- Closed angle forms of glaucoma.
- Diagnosis of acute angle closure, congenital, malignant, or developmental glaucoma.

- Use of <2 or >4 ocular hypotensive medications. (Note: Combination medications count as 2 medications.)
- Use of oral hypotensive medication(s) for glaucoma treatment of the fellow eye.
- Previous incisional glaucoma surgery of any kind, including non-penetrating procedures such as deep sclerectomy or canaloplasty.
- Significant ocular health risk by washout of medication.
- Central corneal thickness >620 or <480 microns.
- Proliferative diabetic retinopathy.
- Previous surgery for retinal detachment.
- Clinically significant corneal dystrophy.
- Previous corneal surgery.
- Previous refractive surgery.
- Degenerative visual disorders such as wet age-related macular degeneration.
- Clinically significant ocular pathology, other than glaucoma.
- Clinically significant ocular inflammation or infection within thirty days prior to screening.
- 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.
- Pregnant, nursing females or women of child-bearing potential who are not using an acceptable method of contraception.

6.0 STUDY PROCEDURES

6.1 Subject Entry, Consent and Enrollment

Participants will be recruited from the Investigators' patient population or referrals. Patients that appear to be eligible will be approached for study participation and sign a patient informed consent (PIC) prior to the commencement of study related procedures.

The investigator or designee will explain the study purpose, procedures, and subject responsibilities to the potential participant. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's willingness and ability to meet the follow-up requirements will be determined. When it has been established that the subject is eligible for possible enrollment into the study, written informed consent will be obtained. One copy of the informed consent form will be retained with the subject's medical records, and one copy will be provided to the subject.

Only one qualified eye per qualified subject may be randomized for treatment. If both eyes qualify for enrollment, the eye with the worse best corrected visual acuity will be designated as the study eye.

6.2 Medication Wash Out

After the subject has successfully completed the preoperative screening exam, he or she will be instructed to discontinue any ocular hypotensive medications in the designated treatment eye for the appropriate washout period, as listed in Table 1, *prior to* the Baseline Exam. If upon washout, the subject experiences an IOP elevation to greater than 39 mmHg, or requires the reintroduction of hypotensive medications or a surgical intervention during the preoperative period, the subject will be treated appropriately and excluded from the study. Any subject whose IOP does not fall within 23-39 mmHg will be exited from the study.

TABLE 1
OCULAR HYPOTENSIVE MEDICATION WASHOUT PERIODS

Carbonic Anhydrase Inhibitors	
Diamox® (Acetazolamide) – oral Rx	14 days
Neptazane® (Methazolamide) – oral Rx	14 days
Azopt® (Brinzolamide)	14 days
Trusopt® (Dorzolamide Hydrochloride)	14 days
Alpha Adrenergic Agonist	
Alphagan® (Brimonidine)	14 days
Iopidine® (Apraclonidine Hydrochloride)	14 days
Beta Blockers	
Betagan® (Levobunolol Hydrochloride)	28 days
Betoptic® (Betaxalol Hydrochloride)	28 days
OptiPranolol® (Metipranolol)	28 days
Timoptic/Betimol® (Timolol Maleate)	28 days
Prostaglandin Analogs	
Lumigan® (Bimatoprost)	28 days
Travatan® (Travoprost)	28 days
Xalatan® (Latanoprost)	28 days
Combined Medications	
Combigan® (Brimonidine Tartrate/Timolol Maleate)	28 days
Cosopt® (Dorzolamide Hydrochloride/ Timolol Maleate)	28 days

6.3 Goldmann Tonometry Procedure

At the baseline, IOP will be assessed using diurnal Goldmann tonometry, after wash-out of hypotensive medications. In this study, 3 IOP readings will be taken during daylight hours as follows:

- Time 1: 9:00 AM (± 1 hour)

- Time 2: 4 hours later (± 1 hour) than Time 1
- Time 3: 4 hours later (± 1 hour) than Time 2

A minimum of 2 IOP readings are to be taken at each time point. If the first two IOP values at a time point are more than 2 mm apart, then a third reading should be taken.

To calculate the mean diurnal IOP, the mean IOP value from each time point is used to calculate a grand average. In the event one or more of the time points requires a third IOP reading, then the median IOP of that time point is used for the calculation of the mean diurnal IOP.

IOP readings taken at screening and at all other follow up visits will be taken once during the visit at 9 AM ± 2 hours. A minimum of 2 IOP readings are to be taken. The mean of these readings will be used for the IOP value at that visit. If the first two IOP readings are more than 2 mm apart, then a third reading should be taken. In this case the median of the 3 values will be used as the value for the visit.

If the subject meets all criteria at the Baseline visit, he or she will be scheduled for surgery within 21 days of this visit. On the day of surgery, the subject will be randomized to either the Hydrus group or iStent group. Computer-generated randomization lists will be used, with separate randomization lists for each clinical site. The subject will not be informed of the randomization assignment and all study personnel will be instructed to maintain the "masking" of the treatment assignments.

6.4 Surgical Procedure

After the subject's group is identified, the patient should receive one Hydrus or two iStents for the study eye. The surgical procedure to implant either the Hydrus or iStent devices should be performed according to the manufacturer's Instructions for Use. Surgery may be performed under either local or topical ophthalmic anesthesia.

6.5 Perioperative Medication

A topical antibiotic and a topical steroid will be administered after surgery. The following dosing regimen is recommended:

1. Moxifloxacin 0.5% (Vigamox® or equivalent), one drop four times per day commencing the day of the procedure and continued for approximately one week postoperatively.
2. Prednisolone acetate 1.0% (Pred Forte® or equivalent), one drop four times per day for one week; followed by one drop three times per day for one week; followed by one drop two times per day for one week; followed by one drop once per day for one week, then discontinue.

Medication to treat transient post-operative spikes in IOP resulting from the use of viscoelastic and surgical manipulation may be required in the immediate postoperative period, as described below.

6.6 Study Visits and Examination Schedule

All subjects will participate in defined follow-up visits through 24 months. A Case Report Form (CRF) shall be completed for each scheduled exam. Unscheduled or interim visits should also be recorded using the appropriate CRF.

The procedures associated with each study visit are outlined and summarized in Appendix 1 (Schedule of Events and Procedures).

6.7 Unscheduled Visits

Any visit to the clinical site, other than those specified in the protocol, at which the subject has a complaint regarding the study eye and/or treatment to the study eye is required or changed will be documented as an unscheduled visit. The Investigator and/or qualified investigational staff will perform the procedures necessary to evaluate the study participant at these visits, and will record the visit in the subject's chart and on an interim CRF. No specific testing is required at interim visit.

6.8 Postoperative Ocular Hypotensive Medications

Since the implantation procedure involves the use of an ophthalmic viscoelastic agent and post-operative steroids, both of which are known to cause IOP elevation in some cases, use of glaucoma medications in the first month after surgery is expected. The first line hypotensive medication in the immediate post-operative period (0-60 days) should be selected from the beta blocker class (if tolerated) as indicated in the table below. In these cases, additional visits may be performed to assess IOP, and medications discontinued if the patient's IOP allows.

Long term medical therapy (defined as medications prescribed at or after the 90-day visit) may be implemented at the Investigator's discretion in order to maintain a safe IOP.

Patient medication usage (medication class, dose, frequency, and brand, if applicable) will be collected at the time of screening. The medications should be assigned a rank order for the purpose of potential reintroduction. If post-operative IOP increases to an unsafe level, ocular hypotensive medications should be reintroduced one at a time and following the order indicated at screening.

If a medication prescribed in the immediate post-operative period does not match the class indicated on the screening list and is continued to the 3 month visit, then the subject should be switched to the pre-surgical medication class and dose if possible.

Reintroduction of ocular hypotensive medication will be recorded in the appropriate Case Report Form, along with the clinical rationale for the decision to apply medications. A record of all medications added, discontinued or changed will be documented on the appropriate Case Report Form.

Because the use of ocular hypotensive medications to control IOP is a study endpoint, the CRF describing the introduction or discontinuation will be reviewed by the Medical Monitor for appropriateness and consistency across study groups. The Medical Monitor will be masked to the identity of the treatment subject.

6.9 Subject Disposition

Subjects may be terminated (exited) from the study early due to:

- Screening failure,
- A threat to the subject's health emerges in the course of following study procedures,
- Inability to continue with the study, and
- Voluntary withdrawal.

Subjects who are terminated due to screening failure will not be followed beyond the date of screening failure. For safety reasons, randomized subjects who are terminated should receive routine clinical follow up until the planned end of the study period. CRF's will not be completed for terminated subjects. Terminated subjects will not be replaced. Notification of a subject's early termination should be made immediately to the sponsor and documented on the appropriate CRF.

Completed subjects are those subjects who have not been terminated from the study prior to completion of follow up.

7.0 ADVERSE EVENTS

All ocular adverse events (AE) in the study eye must be reported on the adverse event CRF. The Investigator must categorize each AE by degree of harm to the subject (mild, moderate, or severe), and the relationship to study device and implantation procedure (not related, possibly, probably, or definitely). Since there are no aspects of the study that can affect both eyes, only serious adverse events observed in the fellow eye will be captured on the case report form throughout the course of the study.

Ocular conditions or diseases that are chronic but stable and meet the inclusion and exclusion criteria should be recorded on the screening CRF under Ocular History. Changes in any chronic condition or disease that are consistent with natural disease progression are not considered AEs and will not be recorded on an AE CRF.

7.1 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:

7.2 Intraoperative Adverse Events

- Hyphema obscuring the surgeon's view
- Choroidal hemorrhage or effusion
- Significant iris injury or trauma
- Corneal edema
- Zonular dialysis

7.3 Postoperative Adverse Events

- Chronic pain in the study eye ≥3 months postoperative
- Flat anterior chamber with lens/cornea touch or with iridocorneal apposition without lens/cornea touch >1 month postoperative
- Best-corrected visual acuity loss of 2 lines (10 letters) or more on the ETDRS chart compared to baseline values, measured at or after 3 months postoperative
- Hypotony (defined as IOP <6 mmHg) at or after 1 month postoperative
- Maculopathy including hypotonic maculopathy
- PAS with device obstruction
- PAS without device obstruction
- Device migration (dislodgement or movement)
- Wound dehiscence (persistent aqueous leak or fistula formation)
- Inflammation (defined as any inflammation requiring treatment with topical, sub-Tenon's or systemic anti-inflammatory medication) lasting longer than 1 month
- Endophthalmitis
- Persistent hyphema of >2 mm present >1 week postoperative
- Corneal opacification
- Corneal decompensation
- Corneal edema persisting >1 month (mild to moderate corneal edema prior to 1 month postoperative is not considered an adverse event)
- Retinal complications (flap tears, retinal detachment, or proliferative vitreoretinopathy)
- IOP spike (elevated mean IOP ≥10 mmHg above the qualifying baseline mean IOP more than 1 month postoperative)
- Events resulting in an unplanned ocular surgical re-intervention (other than paracentesis to relieve pressure prior to 1 week postoperative)
- Phthisis
- Significant foreign body sensation at or after 3 months postoperative
- A change in C/D ratio of ≥0.3 units on slit lamp biomicroscopic examination

- A 2-point worsening to 4+ anterior chamber cells or flare at or after 3 months postoperative, not associated with a pre-existing condition
- A 2-point worsening to severe on the slit lamp examination findings (other than cells and flare) at or after 3 months postoperative not associated with a pre-existing condition
- A 2-point worsening of ocular symptoms to severe or very severe at or after 3 months postoperative not associated with a pre-existing condition

7.4 Recording and Reporting Adverse Events

To improve the quality and precision of acquired AE data, Investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs on the AE CRF. Do not use colloquialisms and/or abbreviations.
- For the purposes of reporting infection/inflammation, the following terms and definitions should be used:

Iritis: Presence of inflammatory cells in the anterior chamber, with or without anterior vitreous inflammation.
- The presence of aqueous flare alone will not be considered to constitute iritis.
- For the purposes of this protocol, the term "iritis" will encompass both cases of iritis without anterior vitreous inflammation (iritis) and those with anterior vitreous inflammation (iridocyclitis).

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

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

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.

7.5 Grading of AEs

AEs are to be graded on a three-point scale (mild, moderate, severe) and reported in detail on the appropriate AE CRF. The definitions are as follows:

- Mild: Discomfort noticed but no disruption of normal daily activity
- Moderate: Discomfort sufficient to reduce or affect normal daily activity
- Severe: Incapacitating with inability to work or perform normal daily activity, and any event resulting in death or requiring rehospitalization

7.6 Adverse Events Requiring Expedited Reporting

Investigators must report all SAEs to Ivantis within 48 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 adverse event CRF. SAEs require expedited reporting to the Sponsor or designee regardless of relationship to the implanted devices.

7.7 Unanticipated Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect (as defined above) on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Any UADE must be reported in writing to the Sponsor within 24 hours of knowledge of that event. The Sponsor will be responsible for informing regulatory authorities and all other Medical Ethics Committees/IRBs and Investigators participating in the study of the UADE.

APPENDIX 1: SCHEDULE OF EVENTS AND PROCEDURES

PROCEDURE	SCREENING[1]	BASELINE	SURGERY	1 DAY POSTOP	1 WEEK POSTOP	1 MONTH POSTOP	3 MONTHS POSTOP	6 MONTHS POSTOP	12[1] MONTHS POSTOP	18 MONTH POST OP	24[1] MONTHS POSTOP
Informed Consent	X										
Medical History and Physical	X										
Ocular Medication Assessment	X	X	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
Manifest Refraction	X	X			X	X	X	X	X	X	X
Goldmann Tonometry	X	**X**		X	X	X	X	X	X	X	**X**
Pachymetry CCT	X								X		X
Gonioscopy (study eye)	X				X	X	X	X	X	X	X
Slit Lamp Exam	X	X		X	X	X	X	X	X	X	X
Humphrey 24-2 SITA Standard	X						X		X		X
Fundus Exam/C:D Ratio	X						X	X	X	X	X
Subject Symptoms Questionnaire											X
Adverse Event Assessment			X	X	X	X	X	X	X	X	X

[1] At the Screening Visit, 12 Month and 24 Month postoperative visits, all assessments will be performed for both eyes.