THE HYDRUS III TRIAL:
A PROSPECTIVE, MULTICENTER, RANDOMIZED COMPARISON OF THE HYDRUS™ AQUEOUS IMPLANT TO THE ISTENT FOR LOWERING INTRAOCULAR PRESSURE IN GLAUCOMA SUBJECTS UNDERGOING CATARACT SURGERY

INVESTIGATIONAL PLAN

NCT02024464

PROTOCOL #: **CP-10-002**
REVISION: **C**
PROTOCOL VERSION DATE: **July 22, 2013**

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[redacted]	

PROTOCOL SIGNATURE PAGE

Protocol Number: CP-10-002-C (HYDRUS III STUDY)

A Prospective, Multicenter, Randomized Comparison of the Hydrus™ Implant to the iStent for Lowering Intraocular Pressure in Glaucoma Subjects Undergoing Cataract Surgery.

I have read this protocol and agree to adhere to the requirements outlined within. I will review and discuss pertinent material with study personnel and ensure they are fully informed of the requirements of this protocol. I will also ensure that this study is conducted in compliance with this protocol, Good Clinical Practice (GCP), and any applicable local or national regulatory agencies and their requirements.

_____
Clinical Trial Site Name and Site Number

_____
Printed Name of Clinical Investigator

_____ _____
Clinical Investigator Signature Date

STUDY OUTLINE

Study Title:	A Prospective, Multicenter, Randomized Comparison of the *Hydrus™ Aqueous Implant* to the *iStent* for Lowering Intraocular Pressure in Glaucoma Subjects Undergoing Cataract Surgery (HYDRUS III Trial)
Study Device:	The CE-marked *Hydrus™ Aqueous Implant* (Ivantis, Inc., Irvine CA)
Control Device:	The *iStent* Trabecular Micro Bypass (Glaukos Inc., Laguna Hills, CA) -- a CE-marked device for the study indication.
Study Population:	Subjects with mild to moderate Primary Open Angle Glaucoma (POAG), pseudoexfoliative glaucoma, or pigmentary glaucoma undergoing cataract surgery.
Study Objective:	Compare the effectiveness of the *Hydrus™ Aqueous Implant* to the *iStent* for lowering intraocular pressure in glaucoma subjects undergoing cataract removal and intraocular lens implantation in the indicated study population.
Study Design And Methods:	A post-market, prospective, multicenter, randomized clinical trial in which potential study participants with a positive diagnosis of POAG, pseudoexfoliative glaucoma, or pigmentary glaucoma and cataract will be screened for eligibility. If eligible criteria are met, the study participants will undergo a screening washout phase during which all glaucoma medications (topical and oral) will be discontinued. Following wash-out, the subjects will return and be evaluated for a fully-washed-out baseline diurnal intraocular pressure (IOP). If the baseline IOP criterion is met, the subjects will be scheduled for cataract surgery and Intraocular Lens (IOL) placement. After successful cataract extraction and IOL placement, subjects will be randomized to receive either a single *Hydrus™ Aqueous Implant* or *iStent.* Interim follow up visits will be conducted at 1, 7, and 30 days, and then at 3, 6, 12, 18 and 24 months where each subject's IOP will be measured and ocular health will be evaluated. The primary endpoint will be diurnal IOP at 12 months as measured by Goldmann tonometry, after wash out of any hypotensive glaucoma medications. There will be a visit at Month 18 and the final study visit will occur at 24 months.

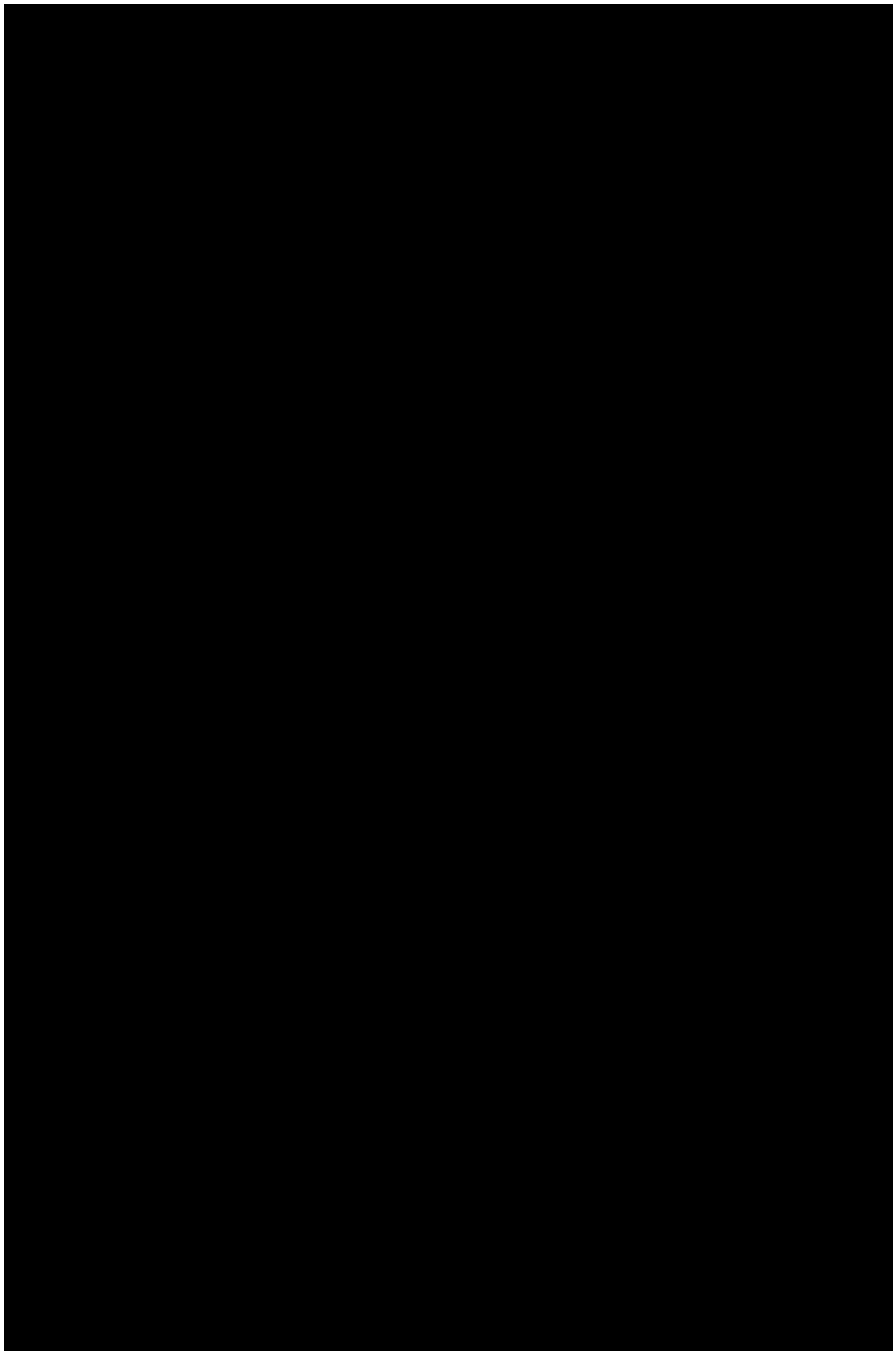
[redacted]

Number of Sites: Up to eight clinical sites in Europe and one in South America.

Selection Criteria: Ocular criteria relates to the study eye only.

Inclusion Criteria:

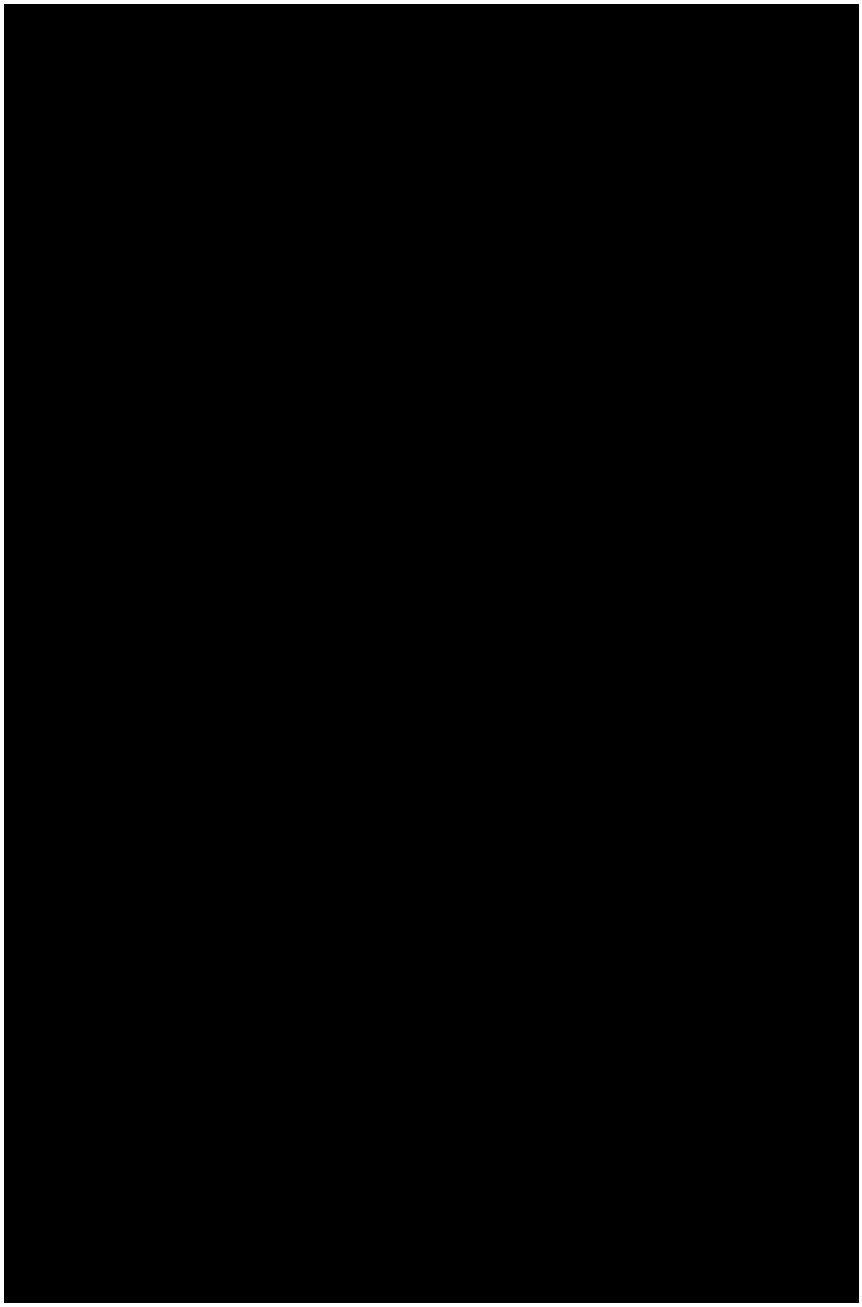
- Male and female subjects, from 21 to 84 years of age.
- A diagnosis of primary open angle glaucoma (POAG), pseudoexfoliative glaucoma (PXG), or pigmentary dispersion glaucoma (PDG).
- [redacted]
- [redacted]
- An operable age-related cataract with BCVA of 20/40 or worse, eligible for phacoemulsification.



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
- Diagnosis of acute angle closure, traumatic, congenital, malignant, uveitis, or neovascular glaucoma.
- Secondary (such as neovascular, uveitic, traumatic, steroid induced, lens induced, or glaucoma associated with increased episcleral venuous pressure), congenital, or developmental glaucoma.
- Previous argon laser trabeculoplasty (ALT). Selective laser trabeculoplasty (SLT) is allowed.



Primary Endpoint:	The primary effectiveness endpoint for this study is diurnal IOP at 12 months following the wash-out of all glaucoma medications.
Secondary Endpoints:	Secondary effectiveness endpoints include • A reduction in IOP of at least 20% following the wash-out, as compared to the washed-out baseline. • An IOP of no less than 5 mm Hg and no more than 18 mmHg at 12 months post washout.
Safety Endpoints:	Safety outcomes include loss of lines of BCVA, results of slit lamp and fundus examination, and the incidence of complications and adverse events.
Statistical Analysis:	Descriptive statistics will be used to summarize subject demographic, procedural, and safety data. [redacted] Secondary endpoints will be evaluated using tests of proportion for subjects meeting the specified endpoints.

1.0 INTRODUCTION AND RATIONALE

Glaucoma is a collection of disorders characterized by progressive loss of visual fields due to optic nerve damage, and is the leading cause of blindness in the U.S., affecting 1-2% of individuals aged 60 and over. Research has determined that the rate of primary open-angle glaucoma (POAG) – the most common form of glaucoma -- in the United States is at 2.2 million people.[1] Based on that figure, it is estimated that between three and six million people in Europe, and approximately 3 million people in South America have elevated intraocular pressure and are at an increased risk for developing POAG. POAG accounts for 90% of all cases of glaucoma. It is a slow, progressive disease that produces no symptoms in its early stages. Although the drainage system of the eye remains open and functions properly, the eye is unable to remove the excess fluid at a pace sufficient to prevent a rise in intraocular pressure (IOP). Progressive vision loss tends to be painless, and subjects often present with advanced disease.

Although there are many risk factors associated with the development of glaucoma (age, race, myopia, family history, and injury), elevated intraocular pressure is the only risk factor that can be successfully treated and that is correlated with the reduction of glaucomatous optic neuropathy. Management of glaucoma requires chronic, lifelong treatment with a spectrum of therapeutic options including medications, laser treatment and microsurgical devices / implants, all with the therapeutic goal of lowering intraocular pressure to target levels in order to prevent loss of visual fields from excessive pressure on the optic nerve.

Historically, first-line treatment for elevated intraocular pressure consists of medical therapy. Results of the Early Manifest Glaucoma Trial (EMGT),[2] the Advanced Glaucoma Intervention Study (AGIS),[3, 4] the Collaborative Initial Glaucoma Treatment Study (CIGTS),[5] the Normal Tension Glaucoma Study (NTG),[6] and the Ocular Hypertension Treatment Study (OHTS) indicate that topical ocular hypotensive medication is effective in reducing intraocular pressure and thus delaying or preventing the progression of POAG.[7]

Several major pharmacologic classes of therapeutic agents are used in the treatment of glaucoma. The mechanism of action consists of either decreasing aqueous fluid production in the ciliary epithelium, improving aqueous outflow via the trabecular meshwork (responsible for 80% of normal outflow) or the uveoscleral route (20%), or a combination of these methods.

While currently available glaucoma medications are generally effective, these drugs are not without side effects. Approximately 5% to 15% of subjects on prostaglandin analogues experience ocular side effects such as hypertrichosis, iris pigmentation, conjunctival hyperemia, and darkening of the periocular skin. These side effects may serve to further discourage subjects from adhering to the dosing regimen. Close to 60% of latanoprost monotherapy subjects experienced adverse events, at a rate of 1.7 events per subject, and 20% of subjects who discontinue latanoprost within first 24 months of treatment cite adverse events as the reason for discontinuation.[8] This rate increased to 1.9 with addition of a beta-blocker and to 2.4 with brimonidine plus a beta-blocker. Adverse events associated with glaucoma medications included toxicity, allergic response, bronchospasm, cardiac failure, depression, impotence.

In the face of the complexity of therapeutic regimens, the chronic use of multiple medications, the need for frequent daily administration, the presence of side effects and the chronic asymptomatic nature of POAG, subjects often do not take their medication consistently. This presents the physician with a significant problem of subject non-compliance.

In a comprehensive review of 76 studies published between 1986-2000, mean drug compliance was found to be approximately 71% (S.D. 17%, range 34%-97%) and declined as the number of daily doses increased.[9] Approximately 12% of glaucoma patients on once or twice daily dosing regimens reported missing a significant number of doses.[10] Patients often underestimate their level of defaulting when questioned. In a study using a pilocarpine eye drop monitor, on average, patients administered 76% of their eye drops, but reported taking 97% of the required dosage.[11] Patients often take their medication as prescribed on the day of a visit to the doctor, but when asked, admit to not taking their medication on a regular basis. A study examining compliance with timolol found that non-complaint patients went a mean of 85 days per year without medication, with a maximum of 165 days.[12]

The ability to administer eye drops, particularly in the elderly, and understanding of the disease and treatment are also important factors. Brown et al (1984) found that even in patients experienced in the use of topical eye drops, 13% were unable to instill topical medications into both eyes successfully despite multiple attempts.[13] Therefore, when combining all of the factors that can affect proper administration of glaucoma medication, the adherence to therapy factor is only 60.5% (79% prescription refilled, drops are instilled correctly 87% of the time, and patients administer the medication in a timely fashion 88% of the time).

Finally, it is known that long-term topical therapy engenders local conditions which may adversely affect the outcome of possible future filtration surgery. Because glaucoma requires lifelong management, there is a concern that prolonged use of medications may ultimately reduce sight saving therapeutic options.[14]

These limitations of glaucoma medications, and the need for continuous long-term follow-up in order to prevent glaucoma progression of glaucoma and potential vision loss, have led to interest in the use of glaucoma implants. Since open-angle glaucoma and cataracts are present with increasing frequency in older patients, and these conditions co-exist in an estimated 20% of cataract surgery patients (CMS published data), the ability to implant a glaucoma device during scheduled cataract surgery offers a unique opportunity for concurrent placement of a glaucoma implant without the risk of an additional intraocular surgical procedure. Implantation of a glaucoma device designed to provide additional lowering of IOP can mitigate issues of drug compliance in elderly glaucoma patients with the continuous treatment offered by an implant. An example of one such implant that has been CE marked and licensed (#80214) in Canada is the *iStent*® Trabecular Micro-Bypass Stent (Glaukos Corporation, Laguna Hills, CA. Model GTS 100L/R). The operating principle of this device is to provide a conduit for aqueous humor through the trabecular meshwork, thereby increasing aqueous flow.

Ivantis has developed the *Hydrus™ Aqueous Implant* for the purpose of decreasing IOP. The Hydrus provides a conduit through the trabecular meshwork and also scaffolds Schlemm's canal, the aqueous collector channel that surrounds the eye. The implanted Hydrus serves to both maintain or dilate Schlemm's canal and provide an opening through the trabecular meshwork to restore the natural outflow pathway of the eye. This dual function may improve IOP reduction compared to the *iStent*.

On 26 May 2011, the *Hydrus™ Aqueous Implant* was granted CE Mark by the National Standards of Authority of Ireland (CE 0050) for the reduction of IOP in POAG subjects.

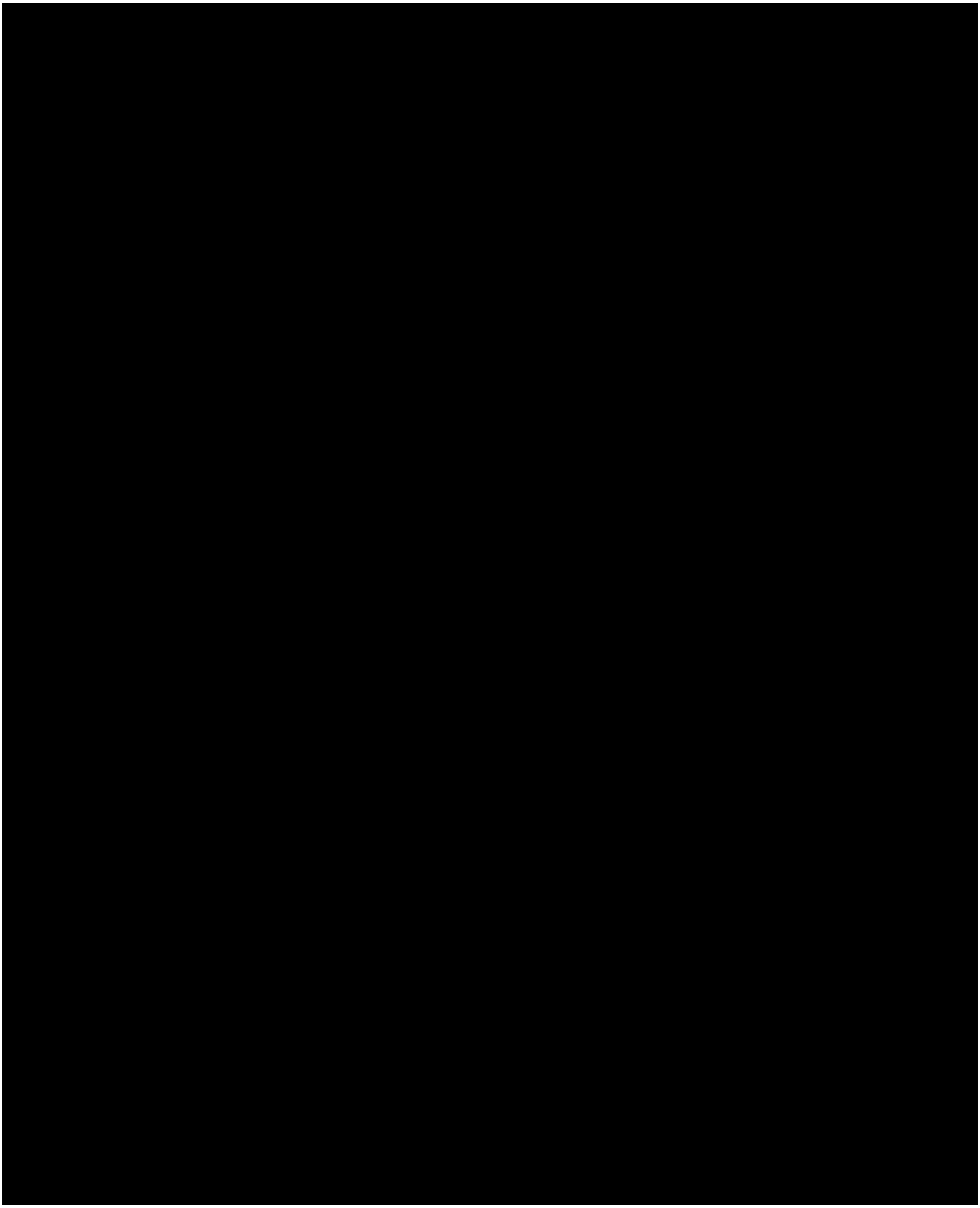


Figure 1: The Ivantis Hydrus Implant

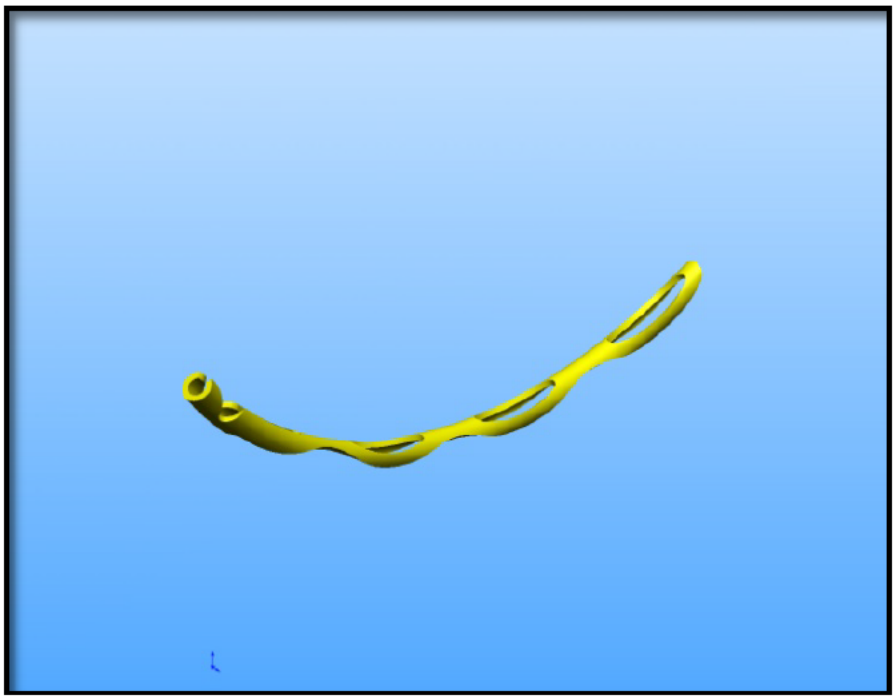


Figure 2: Hydrus implanted within Schlemm's Canal

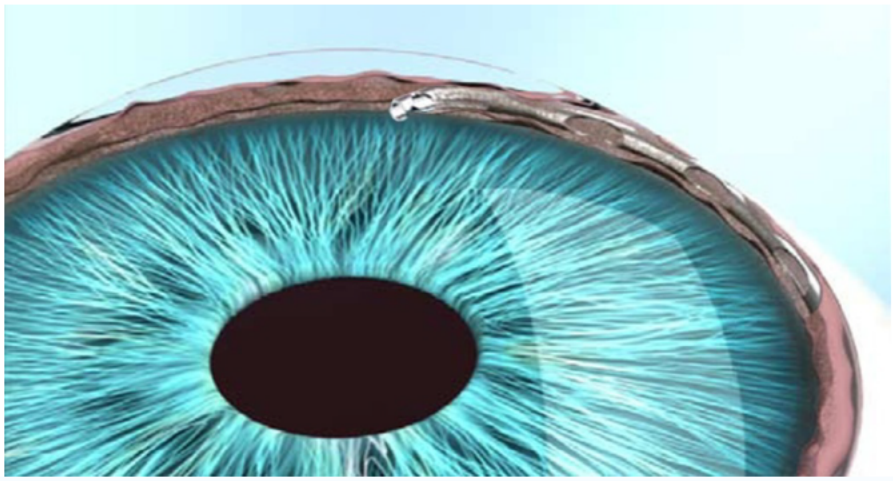
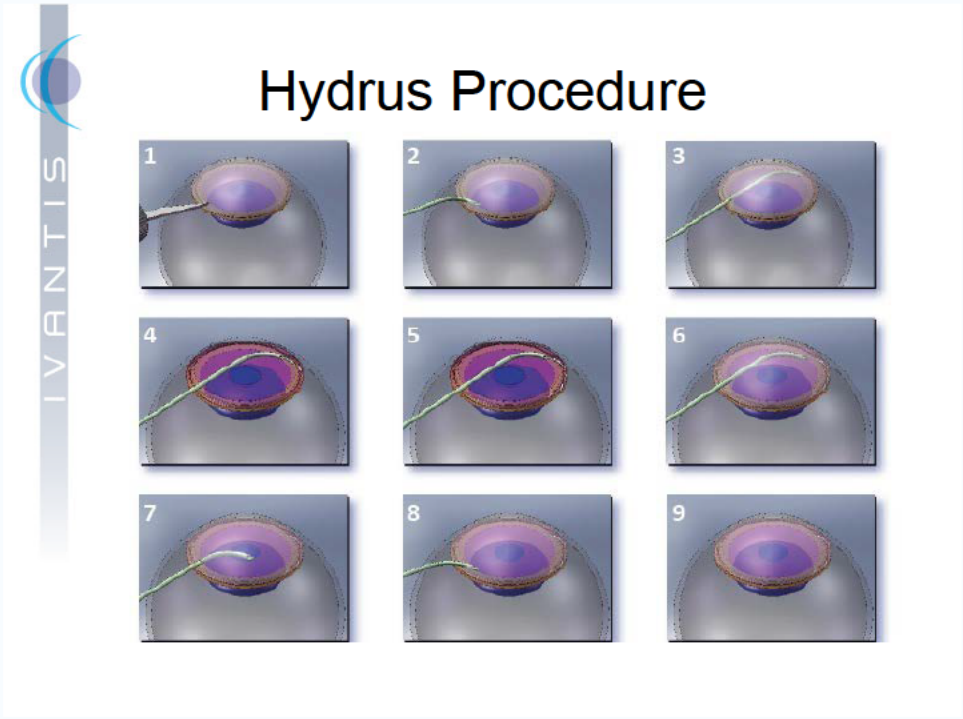
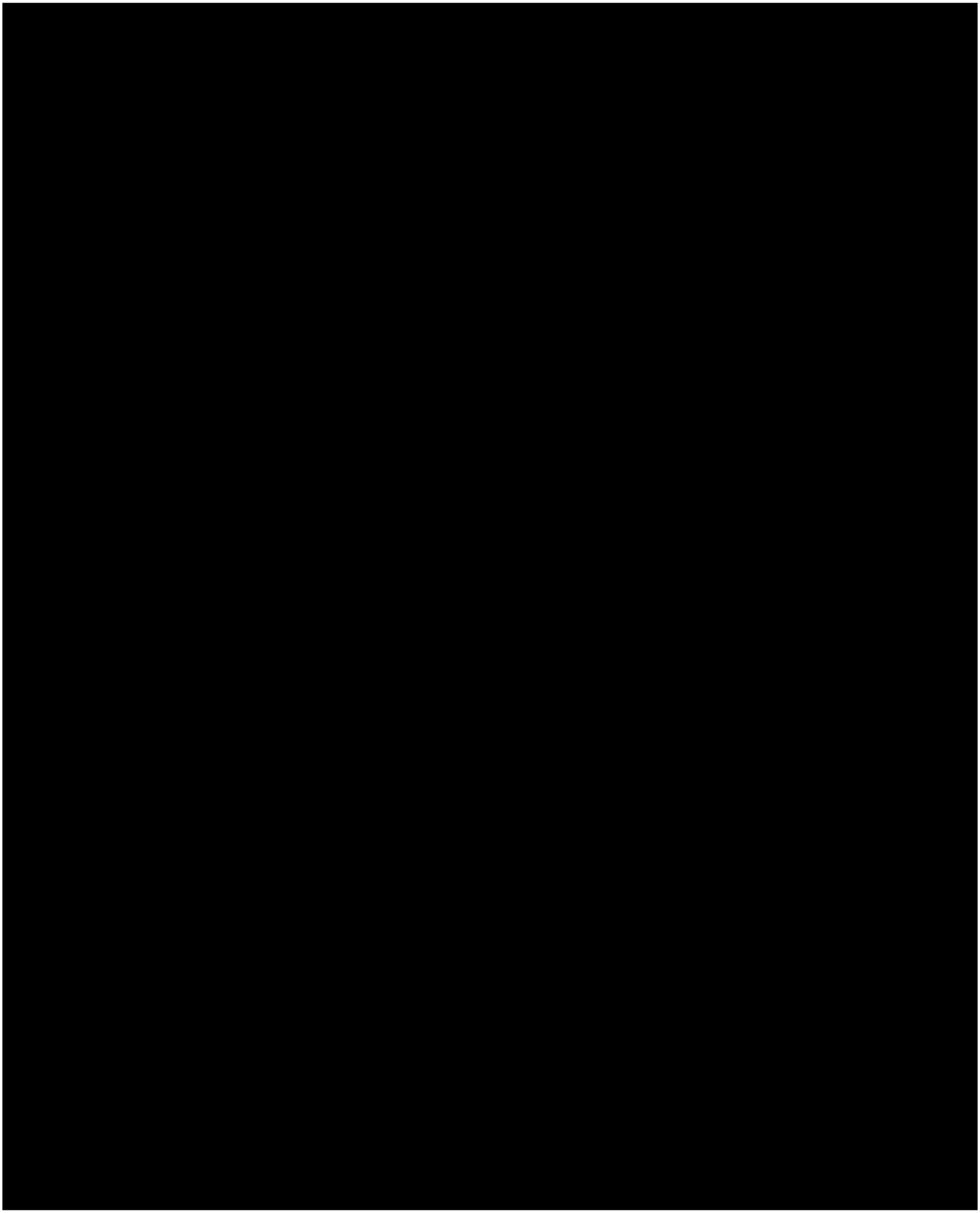


Figure 3: The Hydrus Implant Procedure



Nitinol, a nearly equal part composition of nickel (Ni) and titanium (Ti), is one of a very few alloys that is both highly elastic and biocompatible. Nitinol, which is formed by alloying nickel and titanium (~ 50% Ni), is a shape memory alloy with super elastic properties very similar to those of bone in comparison to the highly limited elasticity of stainless steel, another commonly used biomaterial. Nitinol's super elastic properties also allow delivery of an implant through very tortuous / restrictive passages with minimal force. More importantly, the device will still retain its intended geometry while other metals would be deformed to unintended geometries. These properties make nitinol an especially advantageous material for biomedical applications. Some of the biomedical applications that utilize nitinol include stents, heart valve tools, bone anchors, staples, septal defect devices and implants. It should be noted that nitinol's self-expanding property, or a return to its desired geometry by means of temperature change, a difference between room temperature and body temperature, are not utilized by the Hydrus.



3.0 STUDY OBJECTIVE

The objective of this clinical trial is to compare the effectiveness of the *Hydrus™ Implant* to the *iStent* for lowering intraocular pressure (IOP) in glaucoma subjects undergoing cataract removal and intraocular lens implantation.

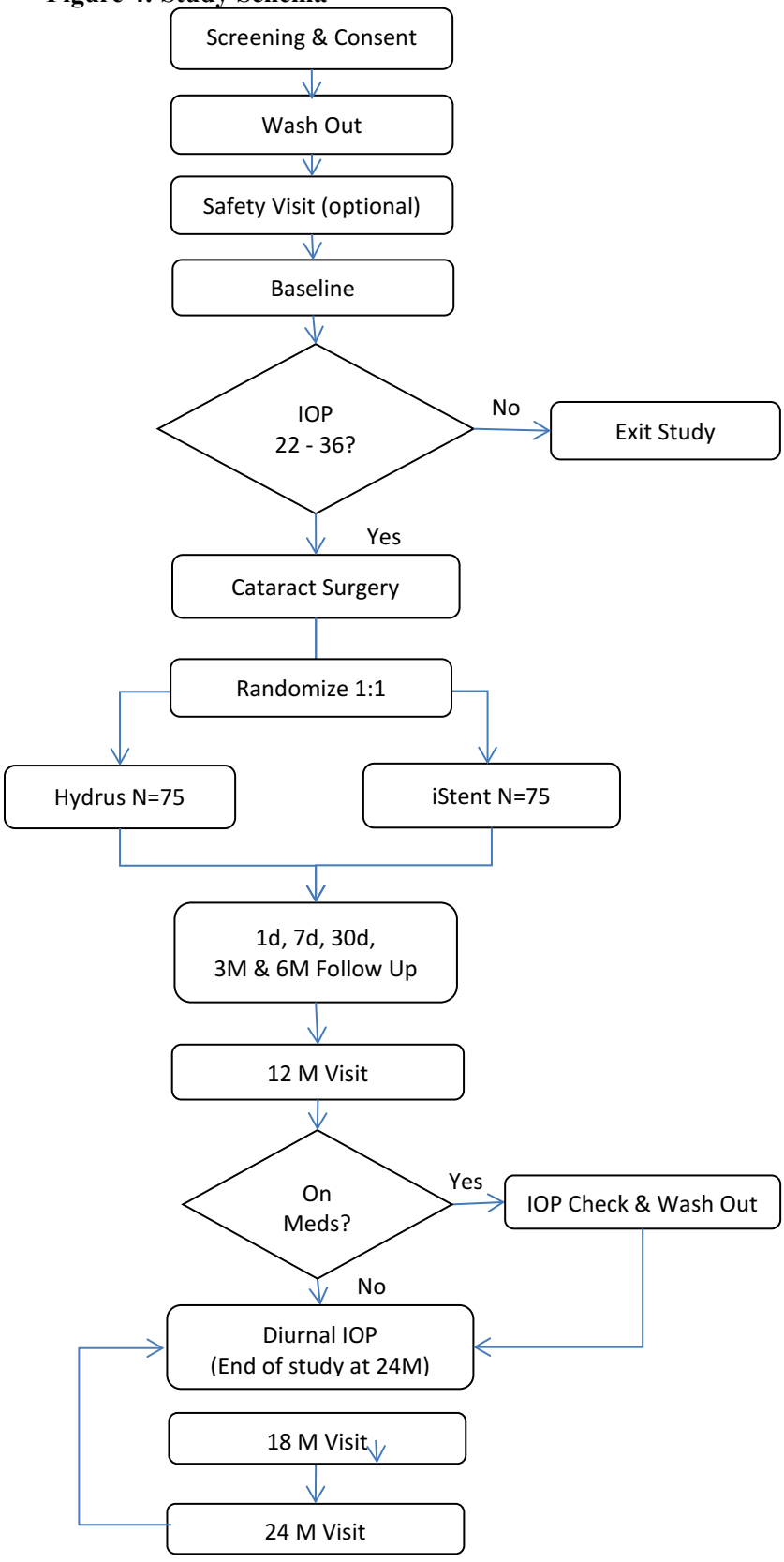
4.0 STUDY DESIGN

This study is a post-market prospective, randomized, controlled, multicenter clinical trial in which a total of approximately 150 subjects will be randomized after successful cataract surgery to receive either the *Hydrus Implant* or the *iStent.* Potential study participants will be consented, at which time they will undergo screening criteria for eligibility. If eligibility criteria are met after initial screening, the study participants will undergo a screening washout phase during which all glaucoma medications (topical and oral) will be discontinued; the duration of the wash-out phase to be determined by the specific medication(s) used by the subjects. Following wash-out, the subjects will return for a baseline evaluation, and if found to continue to meet the eligibility requirements, and agree to participate, will be scheduled for cataract surgery, randomized, and followed up at specified intervals for a 2 year period. The study schema is presented in Figure 4.

Of the two eye implants being used in this study, the *Hydrus™ Aqueous Implant* (the test article) is currently CE marked for use in the EU countries. It is intended for the reduction of intraocular pressure (IOP) in subjects with primary open angle glaucoma (POAG), pseudoexfoliative glaucoma, or pigmentary glaucoma as a stand-alone treatment or in conjunction with cataract surgery. The *iStent* (the control article) is currently CE marked for use in the EU countries. It is intended for the reduction of IOP in POAG subjects with concurrent cataract or in stand-alone treatment, and is thus considered a suitable control.

In the event a study subject does not respond to device therapy, hypotensive glaucoma medications may need to be prescribed during the follow up period to reduce IOP to a safe level, at the discretion of the attending physician. To address the confounding effect of medications on the assessment of the devices' ability to reduce IOP, a "wash-out" of all glaucoma medications will be conducted prior to the 12 and 24 month follow-up visits.

Figure 4: Study Schema



5.0 STUDY ENDPOINTS

The primary effectiveness endpoint for this study is diurnal IOP at 12 months following the washout of all glaucoma medications.

Secondary effectiveness endpoints include:

- A reduction in IOP of at least 20% following the wash-out, as compared to the washed-out baseline.
- An IOP of no less than 5mmHg and no more than 18mmHg at 12 months post washout.

Safety outcomes include loss of lines of BCVA, results of slit lamp and fundus examination, and the incidence of complications and adverse events.

6.0 STATISTICAL METHODS

6.1 Study Hypothesis

Previous clinical research has shown that the risk for glaucomatous progression is significantly reduced when IOP is lowered, [redacted] Thus, a reduction in pressure in the *Hydrus Implant* group compared to *iStent* is anticipated to be clinically relevant. The hypothesis that the Hydrus Implant will lower IOP compared to the *iStent*, is being tested in this study. [redacted]

6.2 Sample Size

The study size is based on the primary endpoint. [redacted]
A power calculation yields a sample size of 65 subjects per arm for a 1:1 randomization ratio. Assuming a 15% loss to follow up at 12 months, a total of 75 randomized subjects are required per arm.

6.3 Safety Analysis

All study subjects randomized in the study will be evaluated for safety outcomes. Frequency tabulations of safety outcomes will be performed at 1, 3, 6, 12, 18 and 24 months

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Male and female subjects who meet the inclusion and exclusion criteria in this protocol, will be eligible for enrollment in this study. *Ocular criteria relates to the study eye only*.

- Male and female subjects, from 21 to 84 years of age.
- A diagnosis of primary open angle glaucoma (POAG), pseudoexfoliative glaucoma (PXG), or pigmentary dispersion glaucoma (PDG).
- [redacted]
- An operable age-related cataract with BCVA of 20/40 or worse, eligible for phacoemulsification.

[redacted]

7.3 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
- Diagnosis of acute angle closure, traumatic, congenital, malignant, uveitis, or neovascular glaucoma.
- Secondary (such as neovascular, uveitic, traumatic, steroid induced, lens induced, or glaucoma associated with increased episcleral venuous pressure), congenital, or developmental glaucoma.
- Previous argon laser trabeculoplasty (ALT). Selective laser trabeculoplasty (SLT) is allowed

8.0 STUDY PROCEDURES

8.1 Subject Entry, Consent and Enrollment

Participants will be recruited from the Investigators' subject population or referrals. Subjects that appear to be eligible subjects will be approached for study participation and sign a subject 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 shall 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 the subject agrees to participate, written informed consent will be obtained, at which time the subject will undergo eligibility requirements, to determine possible enrollment into the study. 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.

Study-specific initial screening tests will then be performed and if all initial screening criteria are met, the subject will be considered enrolled in the study. Approximately 100 subjects will be enrolled in the study; approximately 30% are expected to drop out due to pre- or intra-operative entry criteria, resulting in a 70 subject randomized population.

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 (BCVA) will be designated as the study eye. If the qualifying visual acuity is obtained using the BAT meter, the eye with the worse BCVA will be designated as the study eye. If a subject's study eye fails to qualify for surgery, the subject's fellow eye may be considered for enrollment after the IOP in the study eye is considered to meet the eligibility requirements.

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 2, *prior to* the Baseline Exam. If upon washout, the subject experiences an IOP spike of > 36 mmHg, or requires the reintroduction of hypotensive medications due to an IOP spike, or a surgical intervention during the preoperative period, the subject will be treated and will be considered for withdrawal from the study. However, sites should confirm with Ivantis if there are any questions.

TABLE 2
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

TABLE 2 (Cont'd) OCULAR HYPOTENSIVE MEDICATION WASHOUT PERIODS	
Combined Medications	
Combigan® (Brimonidine Tartrate/Timolol Maleate)	28 days
Cosopt® (Dorzolamide Hydrochloride/ Timolol Maleate)	28 days
Pilocarpine	7 days
Dipivefrin and epinephrine products	28 days

If subjects have not used any ocular hypotensive medications, they may be scheduled for a Baseline Visit up to 45 days after successfully completing the Screening Visit. At the Baseline Visit, upon confirmation of a successful washout, subjects will undergo an evaluation for continued eligibility.

8.2 Cataract Extraction and IOL Replacement

If the subject meets all criteria at the Baseline visit, he or she will be scheduled for surgery within 60 days of completing the Baseline visit. In the period between the baseline visit and the surgery date, the patient may be re-started on hypotensive medications after determination of the washed out diurnal IOP. Cataract replacement surgery will be done with phacoemulsification using standard techniques. IOL's suitable for glaucoma subjects will be selected according to physician or subject preference.

If the subject meets all intraoperative eligibility criteria, randomization to either the *Hydrus* group or *iStent* group will be performed at the end of the cataract extraction and IOL implantation. Computer-generated randomization lists will be used, with separate randomization lists for each clinical site. The site will open the randomization envelope upon completion of an uncomplicated cataract extraction and IOL implantation. 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.

8.3 Surgical Procedure

After the subject's randomization group is identified, the subject shall receive either one *Hydrus* or *iStent*.

If the subject has been randomized to receive the *iStent*, the implant procedure should be performed according to the *iStent* Instructions for Use.

Implant surgery of the *Hydrus* device will be performed in all qualified study subjects randomized into the test arm. Surgery will be performed under either local or topical ophthalmic anesthesia.

Implantation of the Hydrus device will be performed after cataract extraction and IOL implantation as instructed below:

1. Position the subject's head for use of direct gonioprism lens.

2. Place gonioprism lens on the eye to establish a view of the angle. Use ophthalmic viscosurgical device (OVD) as a coupling agent. Verify angle structures including scleral spur and trabecular meshwork to determine target location. Remove gonioprism lens.
3. The corneal incision must be located four clock hours clockwise from the target location for right-handed access (opposite for left-handed access). If the corneal incision used for the cataract procedure is not viable for the introduction of the *Hydrus Implant*, make an additional 1.5mm incision in the corneal limbus. Use an oblique incision angled toward the target location.
4. Inject Healon GV or similar OVD into the anterior chamber unless similar OVD remains from cataract procedure. Verify eye is firm but do not overinflate.
5. Remove the Hydrus delivery device from the packaging and adjust the cannula orientation for proper hand position.
6. Advance *Hydrus Implant* slightly out of the cannula, dip in OVD and retract implant back into cannula.
7. Insert cannula through corneal incision, keeping needle curve parallel to iris to prevent touching iris, lens or cornea when passing across the anterior chamber.
8. Replace gonioprism lens on cornea to establish view of anterior chamber angle and Hydrus cannula tip.
9. Pierce the trabecular meshwork by aiming the cannula tip slightly uphill toward the pigment. After piercing, the cannula tip should slide gently into Schlemm's canal.
10. Advance the device slowly by rolling the advancement wheel. If resistance is felt, stop advancement, retract if necessary and readjust the cannula.
11. Visually confirm Hydrus implant windows entering the canal. The windows should be visible during advancement.
12. When advancement is complete, roll wheel backwards to remove core.
13. After core is removed, disengage the delivery system from the implant by slowly moving the cannula tip away from the canal and remove the cannula from the eye.
14. Verify inlet placement and adjust if necessary using a Sinskey hook.
15. Irrigate and aspirate the OVD from the anterior segment completely.
16. Close the corneal incision per normal practice and verify eye is re-pressurized.

8.4 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®), one drop four times per day commencing the day of the procedure and continued for one week postoperatively.
2. Prednisolone acetate 1.0% (Pred Forte®), 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.

8.5 Device Inventory

Each Hydrus Implant will be traceable via lot number. Lot numbers will be assigned according to date of manufacture and/or sterilization. Records of device shipments will be maintained at the Ivantis, Inc. facility in accordance with Ivantis Inc.'s Quality System and internal procedures. As only Hydrus Implant devices with CE mark clearance will be used in this study, device accountability records will not be required by the site.

8.6 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.

Screening Visit

The subject must sign a subject informed consent prior to the commencement of any study related procedures. Initial eligibility will be determined at the Screening Visit. If the screening criteria are met, the subject will be considered enrolled in the study and will be instructed to discontinue the use of ocular hypotensive medications, according to Table 2, prior to returning for the Baseline Exam. Subjects not using an ocular hypotensive medication may be scheduled for the Baseline Exam up to 45 days after completing the Screening Exam. Ineligible subjects will be exited from the study. The reason for exit will be documented on the Study Summary Form for each enrolled subject.

The following information will be captured at this visit:

- Signed subject informed consent (if not done previously)
- Demographic information, medical history and ocular medications
- Bilateral best corrected visual acuity (Snellen)
- Bilateral manifest refraction
- Bilateral Humphrey 24-2 SITA standard visual field (All required visual fields will be obtained with a Humphrey automated perimeter using the 24-2 SITA standard threshold strategy.)
- Bilateral slit lamp biomicroscopy
- Bilateral IOP with Goldmann tonometer

  NOTE: Any time IOP is performed, two measurements should be obtained for each IOP measurement; if these values are within ± 2 mmHg of one another, the mean of these two readings will be recorded on the CRF. If the first two measurements differ by more than 2 mmHg, a third measurement will be performed, and the median of the three measurements will be used.
- Bilateral dilated fundus examination and C:D ratio assessment Gonioscopy in the study eye (including Shaffer grading for all 4 quadrants)
- Bilateral central corneal pachymetry

Safety Visit

Between the screening visit and the baseline visit, the subject's IOP status may be checked at the discretion of the investigator. Data from this visit will not be collected unless an adverse event occurs. If during the washout period, the subject experiences an IOP spike of > 36 mmHg requiring the use of hypotensive medication or surgical intervention, the subject will be exited from the study.

Baseline

The Baseline visit is performed following glaucoma medication wash-out, to confirm subject eligibility after medications are discontinued. The following information will be captured at this visit:

- Bilateral assessment of any changes in ocular medical history and medications
- Bilateral manifest refraction
- Bilateral ETDRS best-corrected visual acuity
- Bilateral slit lamp biomicroscopyNon-diurnal Goldmann tonometry, fellow eye only
- Diurnal Goldmann tonometry, study eye only, taken at 3 time points:
    - Time 1: 8:00 AM (± 1 hour)
    - Time 2: 4 hours later (± 1 hour) than Time 1
    - Time 3: 4 hours later (± 1 hour) than Time 2.

Mean diurnal IOP will be computed from the three IOP time points. The mean diurnal IOP must be ≥ 22 and ≤ 36 mmHg in order to qualify for the study.

Operative

Surgery will be scheduled after the subject successfully completes the baseline exam, but not more than 60 days after the date of the baseline exam. In the period between the baseline visit and the surgery date, the patient may be re-started on hypotensive medications after determination of the washed out diurnal IOP.

The following information will be collected at this visit:

- Randomization assignment
- Type of anesthesia
-
- Clock hour location of Hydrus insertion
- Viscoelastic used
- Surgical complications
- Intraoperative adverse events (AEs)

1 Day Postoperative

This visit must occur on the first day postoperatively. The following information will be captured at this visit:

- Ocular medications

- Pinhole visual acuity
- Slit lamp biomicroscopy
- Goldmann tonometry at 8:00 AM ± 1 hour
- Adverse events.

1 Week Postoperative (7 ± 2 days)

The following information will be captured for the study eye, unless otherwise noted, at this visit:

- Ocular medications
- Manifest refraction
- ETDRS BCVA
- Slit lamp biomicroscopy
- Goldmann tonometry at 8:00 AM ± 1 hour
- Gonioscopy
- Adverse events.

1 Month Postoperative (30 ± 7 days)

The following information will be captured for the study eye, unless otherwise noted, at this visit:

- Ocular medications
- Manifest refraction
- ETDRS BCVA
- Goldmann tonometry at 8:00 AM ± 1 hour
- Slit lamp biomicroscopy
- Gonioscopy
- Adverse events.

3 Months Postoperative (90 ± 14 days)

The following information will be captured for the study eye at this visit:

- Ocular medications
- Manifest refraction
- ETDRS BCVA
- Humphrey 24-2 SITA standard visual field
- Slit lamp biomicroscopy
- Goldmann tonometry at 8:00 AM ± 1 hour
- Fundus examination and C:D ratio assessment
- Gonioscopy
- Adverse events

6 Months Postoperative (180 ± 21 days)

The following information will be captured for the study eye, unless otherwise noted, at this visit:

- Ocular medications
- Manifest refraction
- ETDRS BCVA
- Humphrey 24-2 SITA standard visual field
- Slit lamp biomicroscopy
- Goldmann tonometry at 8:00 AM ± 1 hour
- Fundus examination and C:D ratio assessment
- Gonioscopy
- Adverse events.

12 Months Postoperative (365 ± 45 days)

The following information will be captured at this visit:

- Ocular medications
- Bilateral manifest refraction
- Bilateral ETDRS BCVA
- Bilateral Humphrey 24-2 SITA standard visual field
- Bilateral slit lamp biomicroscopy Non-diurnal Goldmann tonometry, fellow eye only, at 8:00 AM ± 1 hour
- Diurnal Goldmann tonometry, study eye only, – taken at 3 intervals:
    - Time 1: 8:00 AM (± 1 hour)
    - Time 2: 4 hours later (± 1 hour) from Time 1
    - Time 3: 4 hours later (± 1 hour) from Time 2

NOTE:

- If the subject is not on medications in the study eye, then a diurnal measurement may be taken for the study eye at this visit.
- If the subject is on medications in the study eye, the subject's IOP should be checked at a single time period, and if appropriate, begin wash out of medications in the study eye according to Table 2. After the appropriate time period, a diurnal IOP should be obtained for the study eye.
- **All IOP measurements must be performed within the Month 12 protocol specified window.**
- If the principal investigator deems wash out inappropriate due to safety reasons, a clinical justification must be documented on the appropriate case report form.

- Bilateral dilated fundus examination and C:D ratio assessment
- Gonioscopy for study eye
- Bilateral central corneal pachymetry
- Adverse events

18 Months Postoperative (540 ± 28 days)

The following information will be captured for the study eye, unless otherwise noted, at this visit:

- Ocular medications
- Manifest refraction
- ETDRS BCVA
- Slit lamp biomicroscopy
- Goldmann tonometry
- Dilated fundus examination and C:D ratio assessment
- Gonioscopy
- Adverse events.

24 Months Postoperative (730 ± 45 days)

The following information will be captured at this visit:

- Ocular medications
- Bilateral manifest refraction
- Bilateral ETDRS BCVA
- Bilateral Humphrey 24-2 SITA standard visual field
- Bilateral slit lamp biomicroscopy
- Non-diurnal Goldmann tonometry, fellow eye only, at 8:00 AM ± 1 hour
- Diurnal Goldmann tonometry, study eye only, taken at 3 intervals:
    - Time 1: 8:00 AM (± 1 hour)
    - Time 2: 4 hours later (± 1 hour) from Time 1
    - Time 3: 4 hours later (± 1 hour) from Time 2

NOTE:

- If the subject is not on medications in the study eye, then a diurnal measurement may be taken for the study eye at this visit.
- If the subject is on medications in the study eye, the subject's IOP should be checked at a single time period, and if appropriate, begin wash out of medications in the study eye according to Table 2. After the appropriate time period, a diurnal IOP should be obtained for the study eye.
- **All IOP measurements must be performed within the Month 24 protocol specified window.**
- If the principal investigator deems wash out inappropriate due to safety reasons, a clinical justification must be documented on the appropriate case report form.

- Bilateral dilated fundus examination and C:D ratio assessment
- Gonioscopy for study eye
- Bilateral central corneal pachymetry
- Adverse events.

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

Unscheduled Visits

Any visit to the clinical site, other than those specified in the protocol, will be documented as an unscheduled visit. Examples of unscheduled visits may include a subject complaint regarding the study eye and/or treatment to the study eye is required or changed, or any other visit deemed necessary at the discretion of the clinician. 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.

8.7 Postoperative Ocular Hypotensive Medications

Since the study population is undergoing cataract surgery involving use of an ophthalmic viscoelastic agent and post-operative steroids, both of which are known to cause IOP elevation, use of glaucoma medications in the first month after surgery is expected in some cases. In these cases, additional visits may be performed to assess IOP, and medications discontinued if the subject's condition allows.

Long-term medical therapy may be implemented or additional surgical measures may be performed at any time during the study at the Investigator's discretion in the event it is required. The primary concern of the Investigator and Sponsor at all times is the health and safety of the subjects.

A record of all medications added, discontinued or changed will be documented on the appropriate Case Report Form for each scheduled visit or on a Case Report Form for an Unscheduled (Interim) Visit, if necessary.

8.8 Treatment of the Fellow Eye

The fellow eye should be treated within the site's standard of care. Any enrolled subject – regardless of randomization assignment – may receive CE-marked *Hydrus Implant* treatment as part of the standard of care to the fellow eye in conjunction with planned IOL implantation – following initial randomization and treatment of the assigned eye in the study.

8.9 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 screen failure will not be followed beyond the date of screen failure. For safety reasons, randomized subjects who are terminated shall be followed until the planned end of study period. 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.

9.0 ADVERSE EVENTS (AE)

All medical events, treatments and outcomes will be recorded in the subject's chart as per the site's routine medical practice but not all untoward medical events will be collected on the CRFs.

9.1 Protocol-defined Adverse Events

Adverse events as defined in this protocol include all ocular adverse events (AE) in the study eye. These events 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.

9.2 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:

9.3 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
- Significant iris injury or trauma
- Corneal edema
- Zonular dialysis

9.4 Postoperative Adverse Events

Postoperative adverse events include:

- 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 measured at or after 3 months postoperative
- Hypotony (defined as IOP < 6 mmHg) at or after 1 month postoperative
- Maculopathy including hypotonic maculopathy
- Device obstructed by iris, vitreous, lens, fibrous overgrowth, fibrin, or blood
- Device explantation
- Device malposition, 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)
- Elevated mean IOP ≥ 10 mmHg than the qualifying baseline mean IOP > 1 month postoperative
- Events resulting in an unplanned ocular surgical reintervention (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
- Peripheral anterior synechia
- 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

9.5 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.

9.6 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.

9.7 Adverse Events Requiring Expedited Reporting

Investigators must report any events that meet any one of the following criteria to Ivantis within 48 hours of observing or learning of the event:

- Any adverse event with an outcome of death or blindness.
- Any Serious Adverse Event (SAE) that is **device or procedure related.**
- Any unanticipated adverse device effect (UADE), also called an unanticipated device-related adverse event.

For these expedited event reports, investigators should record all case details that can be gathered within 48 hours on the SAE page of the CRF.

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

- Caused or led to death
- Life threatening
- Required or prolonged inpatient hospitalization
- Site threatening
- Disabling (i.e., the AE resulted in substantial disruption of the subject's ability to carry out normal life functions)
- Resulted in congenital anomaly/birth defect
- Does not meet any of the above serious criteria but may jeopardize the subject or requires medical or surgical intervention to prevent one of the outcomes listed above.

9.8 Unanticipated Adverse Device Effect (UADE) Reporting

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 by phone or fax to the Sponsor within 24 hours of knowledge of that event. The Sponsor will be responsible for informing regulatory authorities and all other IRBs and Investigators participating in the study of the UADE.

9.9 Regulatory Reporting of Adverse Events

Clinical sites are responsible for the reporting of adverse events to their Ethics Committee (EC) in alignment with local EC requirements. As the study sponsor, Ivantis, Inc. will be responsible for required adverse event reporting to all appropriate Regulatory Authorities within reporting requirements.

10.0 DEVICE FAILURE MALFUNCTION

The following definitions clarify device failure and device malfunction:

Device Failure: a device failure has occurred when the cannula is withdrawn without implantation after an attempted deployment (advancement wheel utilized).

Device Malfunction: a device malfunction has occurred if the device does not operate according to the Instructions for Use (IFU).

Should there be a serious adverse event associated with a device failure/malfunction, notify the Sponsor within 48 hours.

Product complaints should be reported to Ivantis, Inc. through the usual Product Complaint Handling system, and the suspect device should be returned to Ivantis, Inc.

11.0 SOURCE DOCUMENTATION

Any information collected at the time of the subject visit is considered source documentation. In order for information to be considered as a source document (e.g., chart notes, visual field printouts Nerve Fiber Imaging printouts, etc.), it should be part of the subject's permanent medical record.

12.0 DATA COLLECTION AND ANALYSIS

13.0 CASE REPORT FORMS WILL BE PROVIDED TO THE CLINICAL SITES BY THE SPONSOR. SITE CLINICAL RESEARCH COORDINATORS OR INVESTIGATORS WILL TRANSFER DATA FROM SOURCE DOCUMENTS TO THE CASE REPORT FORMS. IVANTIS WILL PROVIDE EACH STUDY SITE WITH A STUDY MANUAL AND TRAINING ON DATA COLLECTION. STUDY MONITORING

Ivantis personnel (or their representative/designee) will monitor this clinical study in a manner consistent with applicable health authority regulations.

1. Ivantis personnel/designee may meet with investigator(s) prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol.
2. Ivantis personnel/designee may meet with the investigator(s) to perform a site initiation visit in which this visit may be at the time study subjects begin to be enrolled. This visit is to ensure that study is ready to begin, subjects are being properly selected, and that study data are being correctly recorded.
3. Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings
4. Ivantis personnel/designee may visit the clinical site when all subjects have completed the final visit of the study to collect the Case Report Forms, source documents, and any other required documents in order to closing out the site.

14.0 RECORDS RETENTION

Investigational sites must keep all records (case report forms, regulatory binder, subject records, source documentation) pertaining to the Ivantis clinical investigation for either a period of at least two years after the trial is complete, or as long as local regulatory requirements dictate. Ivantis will make arrangements for storage of records at the request of the investigator.

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APPENDIX 1: SCHEDULE OF EVENTS AND PROCEDURES (HYDRUS III REV C)

PROCEDURE	SCREENING[1]	BASELINE[1]	SURGERY	1 DAY POSTOP	1 WEEK POSTOP	1 MONTH POSTOP	3 MONTHS POSTOP	6 MONTHS POSTOP	12[1] MONTHS POSTOP	18 MONTHS POSTOP	24[1] MONTHS POSTOP
Informed Consent	X										
Demographics	X										
Medical History	X	X									
Medication Assessment	X	X	X	X	X	X	X	X	X	X	X
Randomization			X								
BCVA - Snellen	X										
Visual Acuity-Pinhole				X							
Manifest Refraction	X	X			X	X	X	X	X	X	X
BCVA (ETDRS)		X			X	X	X	X	X	X	X
Goldmann Tonometry	X	X[2]		X	X	X	X	X	X[2]	X	X[2]
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		X
Fundus Exam/C:D Ratio	X						X	X	X	X	X
Adverse Event Assessment			X	X	X	X	X	X	X	X	X

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

[2]Following washout of hypotensive medication(s), three IOP measurements will be performed at 8:00 AM (± 1 hour), 4 hours (± 1 hour) later, and again 4 hours (± 1 hour) later.

[3]A Safety visit during the washout period between the Screening and Baseline visits is optional.

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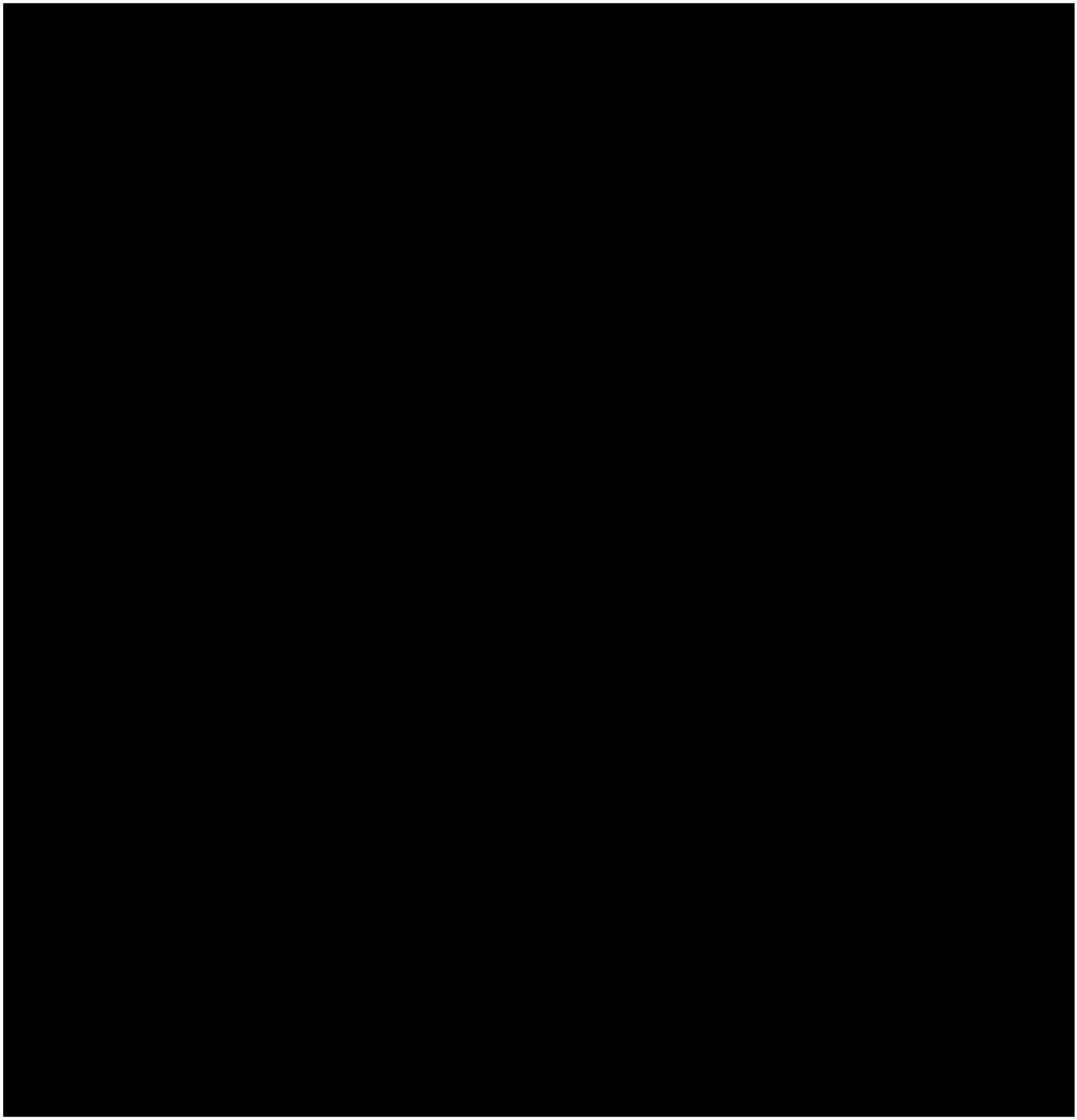

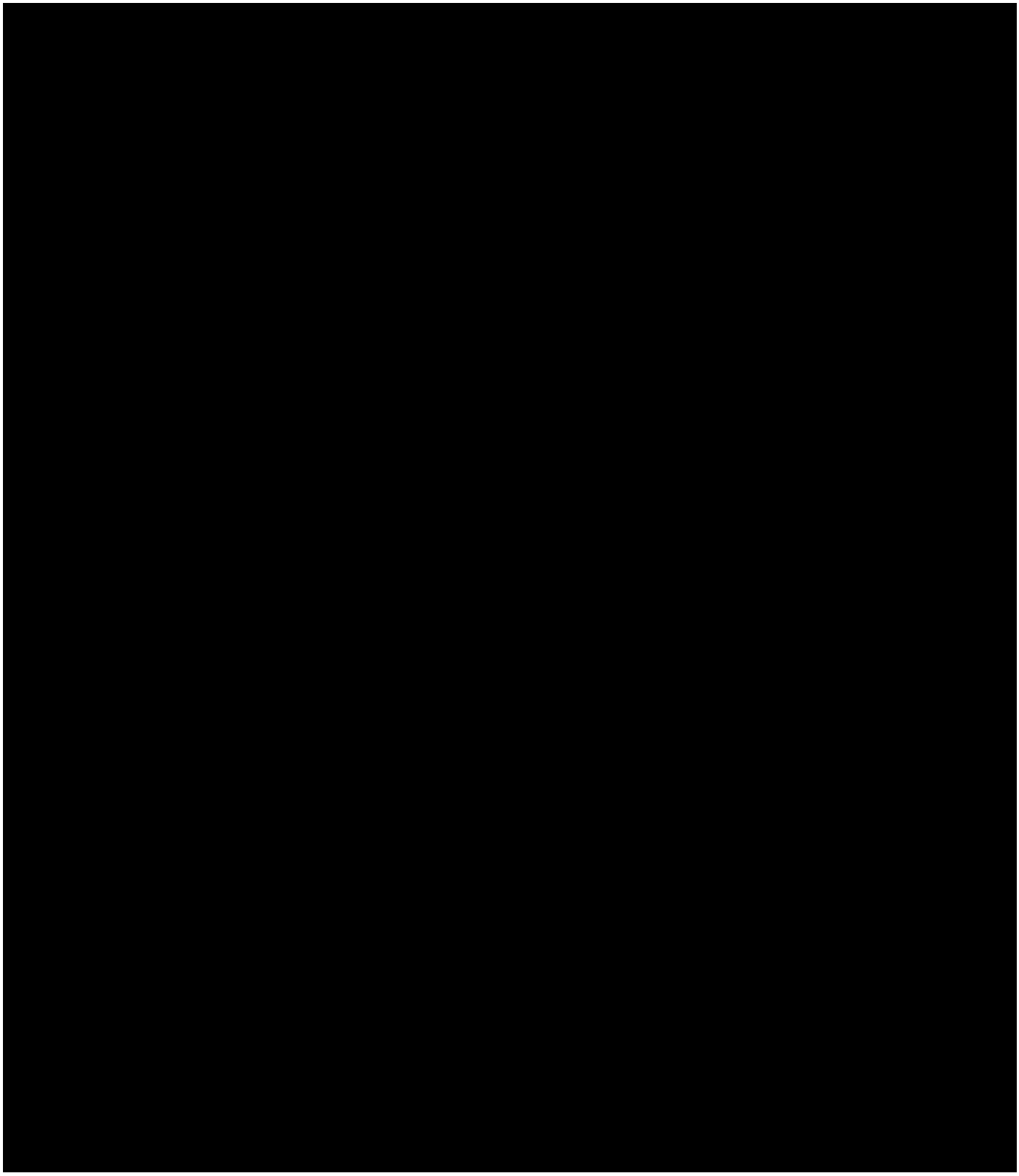

APPENDIX 3: SPONSOR'S COMMITMENTS

Ivantis, Inc. is committed to:

1. Complying with the Declaration of Helsinki, and all applicable health authority regulations governing the conduct of clinical research studies.
2. Protecting the rights, health, safety and welfare of study subjects.
3. Informing the clinical investigators of any new information about the study, which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.
4. Providing the clinical investigators with the study protocol, and a full set of Case Report Forms on which to document the study evaluation variables for each subject entered into the study.
5. Certifying that IRB/EC approval of the protocol and Investigator's Agreement will be completed prior to treatment at an investigational site.
6. Complying with ISO 14155-1:2003/(R) 2008.

APPENDIX 4: INVESTIGATOR'S QUALIFICATIONS AND RESPONSIBILITIES

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

A. Subject Selection

The investigator is responsible for assuring that all subjects entering the study conform to the subject selection criteria.

B. Informed Consent

The investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with prospective subjects prior to their enrollment in the study. The investigator is responsible for obtaining written Informed Consent for each subject, prior to enrollment in the trial. A copy of the signed Informed Consent Form will be maintained in the subject's medical record, a copy of the signed Informed Consent Form will become an integral part of each Case Report file provided to the Sponsor, and a copy will be provided to the subject.

C. Institutional Review Board (IRB) / Ethics Committee (EC) Approval

The investigator must obtain approval for his/her participation in this protocol from the IRB/EC for the institution at which the procedure will be performed, prior to entering any subjects in the study. The Informed Consent document to be used will also be submitted by the Investigator to the IRB/EC for approval prior to initiation of the study. Assurance that the IRB/EC approval of the study protocol and Informed Consent has been obtained will be provided to the Sponsor prior to initiation of the study.

The Investigator must keep the IRB/EC informed of the progress of the study at least annually.

D. Subject Evaluations and Data Reporting

The investigator is responsible for performing the subject evaluations as described in the study protocol. All information generated by the subject evaluation will be recorded on the Case Report Forms provided by the Sponsor, and a copy of supporting source documents will be filed with the CRFs. Case Report Forms will be filled out in ink. Any corrections will be made by lining out, dating and initialing. Correction fluid will not be used. The Enrollment, AE, and Exit CRF pages will be signed and dated by the investigator when each subject completes the study confirming that he or she has reviewed and agrees with all data recorded in the CRF booklet. Upon monitoring visits, each original form will be returned to IVANTIS or its designee along with a copy of the associated source documents. Copies of all Case Report Forms will be retained at the study site in order to be available for monitoring by IVANTIS or its designee.

Investigator(s) will not deviate from the study protocol without prior approval of IVANTIS unless protection of the health, safety or welfare of study subjects requires prompt action.

E. Clinical Trial Material Accountability

The investigator must maintain accurate records of the receipt of all investigational material provided by IVANTIS or its designee. In addition, accurate records must be kept on the amount and date that investigational material was used or returned for each subject in the trial. In addition, a separate area on the Case Report Form for each subject will be provided for the purpose of maintaining this record.

Only *Hydrus Implant* devices with CE mark clearance will be used in this study. Device accountability records will not be required by the site as the device is non-investigational.

APPENDIX 5: DECLARATION OF HELSINKI

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

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the subject's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory

requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on subjects or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious subjects, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the

specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

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

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the subjects who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the subjects who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, subjects entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study or the subject's decision to withdraw from the study must never interfere with the subject-physician relationship.
35. In the treatment of a subject, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the subject or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.