PROTOCOL TMI-13-01 / NCT02448875
VERSION D

RANDOMIZED PROSPECTIVE CLINICAL EVALUATION OF THE SAFETY AND EFFECTIVENESS OF VISCO-ASSISTED CYPASS IMPLANTATION IN PATIENTS WITH OPEN ANGLE GLAUCOMA

SPONSOR:

TRANSCEND MEDICAL, INC
127 INDEPENDENCE DRIVE
MENLO PARK, CA 94025
USA
PHONE: 650-223-6600

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I have read and agree to follow the study procedures as outlined in this protocol.

_____
Investigator Name (Printed)

_____ _____
Investigator Signature Date

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RANDOMIZED PROSPECTIVE CLINICAL EVALUATION OF THE SAFETY AND EFFECTIVENESS OF VISCO-ASSISTED CYPASS IMPLANTATION IN PATIENTS WITH OPEN ANGLE GLAUCOMA

1. PERSONNEL AND FACILITIES

Study Sponsor:

Transcend Medical, Inc.
127 Independence Drive
Menlo Park, CA 94025
USA
Phone: 650-223-6600

2. STUDY SYNOPSIS

2.1 Objective

The purpose of this research study is to assess the safety and effectiveness of visco-assisted CyPass Micro-Stent implantation for the lowering of intraocular pressure (IOP) in patients with open angle glaucoma (OAG).

2.2 Population

Up to 150 eyes meeting subject eligibility criteria listed in Section 5 of the protocol will be randomized to study treatment at up to 5 investigational sites.

2.3 Design

This is a prospective, randomized, controlled, multicenter, interventional study performed in two phases, as follows:

Dose Selection Phase: During this phase, the first cohort (Cohort 1) of 60 subjects will be randomized (1:1:1) to receive either a CyPass Micro-Stent with 30 µl adjunct Healon 5 viscoelastic, a CyPass Micro-Stent with 60 µl of adjunct Healon 5 viscoelastic, or a CyPass Micro-Stent without adjunct viscoelastic. After completion of at least 3 months follow-up on all subjects in this phase, an interim review of safety and efficacy data will be performed to determine the optimum dose of adjunct viscoelastic for the study expansion phase.

Expansion Phase: After the dose selection phase, the study will be expanded to include a second cohort (Cohort 2) of up to 90 additional subjects who will be randomized 1:1 to either the CyPass Micro-Stent without adjunct viscoelastic or to the CyPass Micro-Stent with 60 µl adjunct viscoelastic(the dose selected based on Dose Selection Phase results).

2.4 Primary Endpoint

Proportion of eyes with ≥ 20% decrease in IOP from baseline up to 12 months post-operatively without use of IOP lowering medications.

2.5 Secondary Endpoints

- Rate of intraoperative and post-operative device related ocular adverse events up to 12 months postoperatively
- Mean change in medicated IOP from baseline to 12 months postoperatively

- Proportion of eyes using ocular hypotensive medications at 12 months postoperatively
- Mean number of topical IOP lowering medications at 12 months postoperatively as compared with baseline.

2.6 Schedule of Visits and Examinations

- Screening, Baseline, Operative, Day 1, Week 1, Months 1, Month 3, Month 6,Month 12 and Month 12 Washout (if subject is using ocular hypotensive medication at the Month 12 visit) postoperative. (Parameters per Appendix 1 – Study Examinations and Procedures)

3. INTRODUCTION AND RATIONALE

3.1 Background

Glaucoma is one of the leading causes of blindness in the world.[1] Findings of epidemiological investigations and risk factor analyses provide a framework for consideration of the cause and management of primary open angle glaucoma (POAG), which is as follows:

- Elevated intraocular pressure (IOP)
- Increased age
- Family history of glaucoma
- African or Hispanic/Latino descent
- Reduced central corneal thickness[2,3]

While the relationship between IOP and vision loss is fundamental to all current therapy for OAG, there are several other factors (e.g., blood supply to the optic nerve, substances toxic to the optic nerve or retina, axonal or ganglion cell metabolism, and the lamina cribosa extracellular matrix) that may play a role in the progressive loss of vision due to glaucoma. When IOP is uncontrolled, permanent and irreversible loss of vision due to optic neuropathy can result.

Because elevated IOP is treatable, one can expect to inhibit progression of glaucomatous optic neuropathy by lowering the IOP. Results from randomized controlled trials and other studies reinforce this expectation and provide evidence that successful IOP lowering prevents or delays functional vision loss from glaucoma. [4-22]

In patients with glaucoma, it is generally assumed that the target IOP should be ≥ 20% lower than the pretreatment IOP. Further reduction of the target IOP may be justified by the severity of existing optic nerve damage, the pretreatment IOP, the rapidity with which optic never damage has occurred and other risk factors. In general, the more advanced the optic nerve damage, the lower the target IOP should be. During 7 years of follow-up, patients from the Advanced Glaucoma Intervention Study whose IOP was consistently < 18 mmHg had minimal visual field loss progression on average as compared with patients who had higher IOPs. [23]

Since IOP is homeostatically maintained by the balance of aqueous production with aqueous outflow, current medical therapies for IOP reduction work by either reducing aqueous production, or increasing aqueous outflow.

Surgical therapies for IOP reduction are almost exclusively intended to increase aqueous outflow by either creating an alternate or improved pathway to Schlemm's canal, or by directing outflow to an alternative drainage site outside the intraocular environment. Trabeculectomy and implantable glaucoma shunts have been the mainstay of conventional glaucoma surgery for more than 20 years. In most patients, the clinical effect of each procedure is relatively similar and results in significant IOP reduction, which is sustained for several years.

Trabeculectomy and glaucoma shunts, however, are generally relegated to the end-stages of the glaucoma disease spectrum, largely due to the associated intraoperative and postoperative safety profile of the procedures. Overall, the cumulative rate of significant ocular complications and adverse events may exceed 25 – 30% and, in many cases, these complications lead to visual deterioration, secondary surgical revision or rescue intervention. Additionally, the median failure rate within the first year after surgery exceeds 20% at one year, with progressive attrition of effect in subsequent years. [24]
Such limitations of conventional filtering and glaucoma shunt surgery have led to new, less invasive surgical approaches for IOP reduction such as the implantation of the CyPass Micro-Stent.

3.2 Rationale for the CyPass Micro-Stent

The CyPass Micro-Stent is a small tube made of polyimide, a material previously used in marketed ophthalmic implants. The device, which is described in Section 4 of this protocol, functions by means of its through-lumen. The principle behind device design is outlined in the following discussion of aqueous outflow physiology of the human eye.

Aqueous fluid is produced at the rate of approximately 2-3 µl per minute by the secretory epithelium of the ciliary body, which extends circumferentially around the interior of the eye posterior to the iris and covers the ciliary processes. Aqueous circulates anteriorly through the pupil and exits the eye by means of several independent pathways, including the trabecular, or canalicular, outflow pathway (the major outflow pathway that accounts for a very large percentage of aqueous outflow in the normal eye) and the uveoscleral outflow pathway.
With the trabecular outflow pathway, aqueous passes through the trabecular meshwork into Schlemm's canal, then into aqueous veins that drain into the episcleral venous plexus. The pressure in these veins is generally around 10 mmHg. This outflow pathway is known as "pressure dependent".

The uveoscleral outflow pathway is "pressure independent". With uveoscleral outflow, aqueous moves from the anterior chamber through the intermuscular spaces of the ciliary muscle into the supraciliary and suprachoroidal spaces, then out of the eye through the substance of the sclera or the perivascular spaces of the emissarial channels (perforation in the sclera for the passage of nerves and blood vessels) at a rate of about 0.2 – 0.5 µl per minute.[25] In monkeys, the posterior suprachoroidal pressure is 4 mmHg lower than the anterior chamber pressure. Aqueous flows from the anterior chamber into the supraciliary and suprachoroidal spaces because of this pressure gradient, which is due to the high oncotic absorptive potential of uveal vessels.[26]

While in normal eyes the uveoscleral outflow may provide much less than 50% of total outflow, uveoscleral outflow may have a higher capacity for reduction of IOP in glaucomatous eyes. Experience from glaucoma pharmacotherapy demonstrates that some of the most effective topical therapies for IOP reduction act primarily by increasing uveoscleral outflow.[27]

The CyPass Micro-Stent is designed to facilitate aqueous flow from the anterior chamber into the supraciliary and suprachoroidal spaces of the eye by bypassing the ciliary body and creating a stented cyclodialysis into the supraciliary space. Cyclodialysis clefts, whereby the ciliary body is separated from the scleral spur due to trauma, cataract surgery, or as an intentional surgical therapy for glaucoma have been studied previously. Cyclodialysis creates an additional path between the anterior chamber and the supraciliary and suprachoroidal spaces, which markedly enhances outflow through the posterior portions of the uveoscleral pathway[28]; however, the creation of a cyclodialysis cleft for IOP reduction may result in surgical trauma, hypotony (IOP < 5 mmHg, which may be associated with ciliochoroidal detachment) and spontaneous cleft closure, which may lead to a sudden rise in IOP.

The advantages of the CyPass Micro-Stent over simple surgical cyclodialysis reside in the device's ability to predictably lower IOP to a safe level and to maintain a lower IOP over time.

3.3 Rationale for Visco-Assisted CyPass Micro-Stent Implantation

Clinical data from serial anatomic assessments of the supraciliary cleft post CyPass Micro-Stent implantation provide evidence regarding the benefit of structural stabilization of the ciliary space around the distal portion of the Micro-Stent. Ahmed et al reported a statistically significant positive correlation between the size of the supraciliary cleft around and distal to the CyPass Micro-Stent and the IOP lowering effect.[29] Patients who had larger space formation around the Micro-Stent (clinical

grade 3 – 4), as established via serial OCT imaging, had a more pronounced and sustained IOP effect than patients with a smaller space formation about the Micro-Stent (clinical grade 0-2). This finding is consistent with the physiologic rationale of supraciliary and suprachoroidal flow dynamics whereby aqueous outflow is related to the absorptive capacity of the surrounding supraciliary and suprachoroidal spaces.[30]

As assessed by OCT, the size and nature of the supraciliary cleft around and distal to the CyPass Micro-Stent appears to vary depending on the plasticity and compliance of the ciliary tissue and the surgical dissection forces at the time of Micro-Stent implantation. It is believed that achievement of a more predictable, consistent and volumetrically discrete supraciliary cleft around and distal to the CyPass Micro-Stent may be facilitated via delivery of a standardized volume of ophthalmic viscoelastic to the supraciliary space immediately distal to the Micro-Stent at the time of device implantation. This viscoelastic "spacer" may provide sustained anatomic stability of the area around the device to facilitate enhanced absorptive flow of aqueous.

The use of viscoelastic as a "spacer" is supported by preclinical animal data in cyno models where Klemm et al reported on 12 eyes of 6 owl monkeys in which visco-assisted cyclodialysis was performed by injecting 50-80 µl of hyaluronic viscoelastic into the ciliary cleft.[31] The procedure was safe, without any associated intraoperative or post-operative ocular adverse events. The cleft opening was maintained through the maximum follow up of 140 days. Another cyno study showed the safety and feasibility of visco-assisted cyclodialysis formation without any associated adverse effects [32]

Transcend Medical conducted a study in New Zealand white rabbits to characterize the safety of the visco-assisted CyPass Micro-Stent implantation. In this study, 14 eyes of 7 rabbits were randomized to CyPass Micro-Stent implantation either with or without concurrent delivery of 50 µl of Healon® 5 sodium hyaluronate ophthalmic viscoelastic through the Micro-Stent Applier guide wire posterior to the Micro-Stent's distal end. Ocular safety was assessed at multiple intervals up to 28 days postoperatively and a histologic evaluation was done at study completion. The there were no device-related adverse events and the histological evaluation showed no adverse tissue reaction or morphologic changes related to the injection of viscoelastic.
The visco-assisted CyPass Micro-Stent implantation system is designed to provide precision-guided, targeted delivery of Healon 5 viscoelastic to the space surrounding the distal end of the Micro-Stent via the modification to the Applier guide wire injection system. The CyPass Micro-Stent, the Micro-Stent

Applier guide wire dimensions and flexibility, and Micro-Stent implantation technique are all unchanged. Healon 5 is a highly purified, noninflammatory, high molecular weight fraction of sodium hyaluronate, which is commonly used in conjunction with intraocular surgery as an aid to maintain the anterior chamber or to gently separate, maneuver and hold tissue.[33]

4. CYPASS MICRO-STENT SYSTEM MODEL 231

4.1 Device Description

The CyPass System 231 consists of one (1) CyPass Micro-Stent (Model 2FX) contained in a loader and one (1) CyPass Applier (Model 231).

The CyPass Micro-Stent (Figure 1) is an implantable polyimide tube with a through-lumen designed to provide a permanent conduit for aqueous outflow from the anterior chamber of the eye into the supraciliary and suprachoroidal spaces.

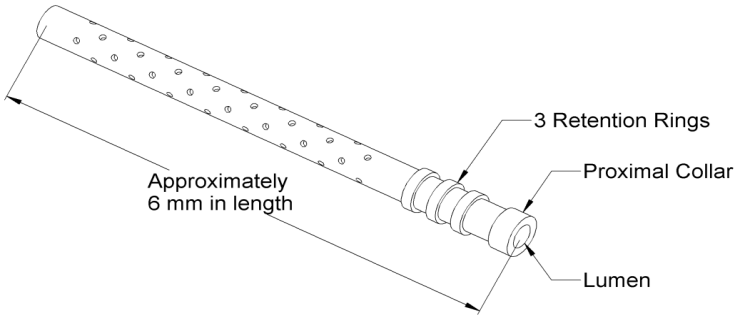


Figure 1: CyPass Micro-Stent, Model 2FX

When implanted as directed in the product labeling, the CyPass Micro-Stent's proximal end resides in the anterior chamber while the distal end rests against the sclera in the supraciliary space.

The CyPass Micro-Stent Applier (Figure 2) consists of a medical-grade polymer hand piece containing an implant delivery guide wire. The guide wire is a pre-shaped nitinol wire with a blunt tip and curved radius at the distal end to facilitate locating and blunt-dissecting the tissue plane between the ciliary body and sclera. The guide wire is supported within a stainless steel guide wire tube. The CyPass Micro-Stent is loaded onto the extended guide wire prior to implantation, such that the Micro-stent's proximal end rests against the guide wire tube.

By connecting the male luer fitting of the Healon 5 viscoelastic syringe to the female luer fitting on the CyPass Applier, the Applier can be used to deliver the viscoelastic to the desired location in the eye.

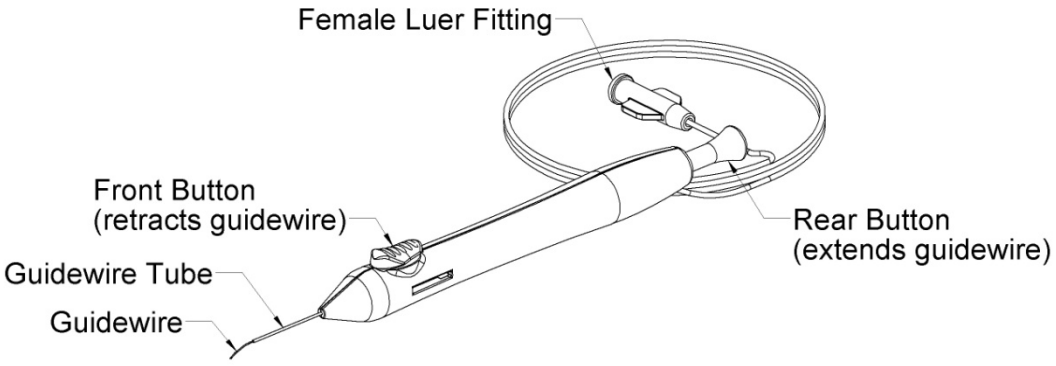
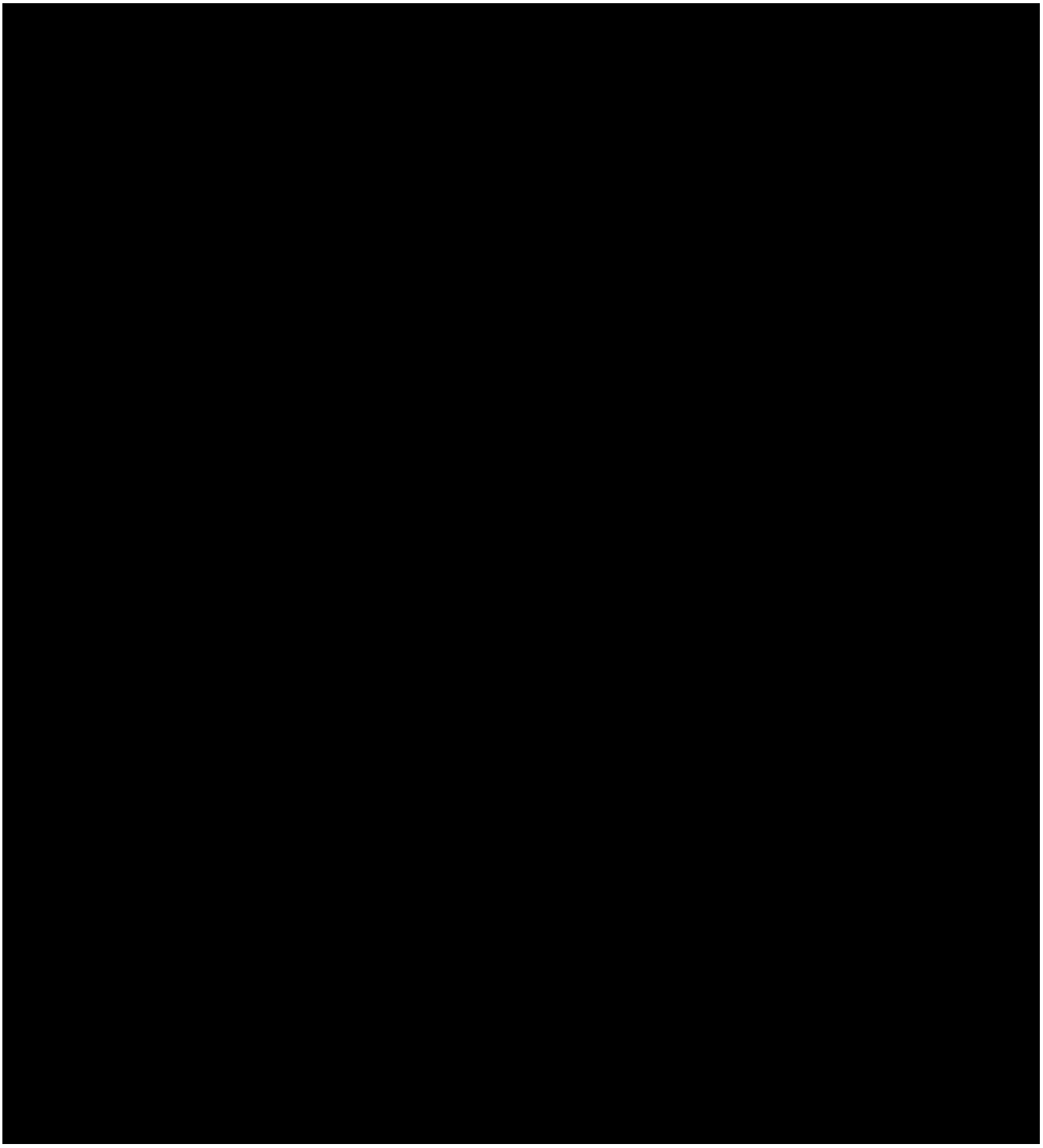
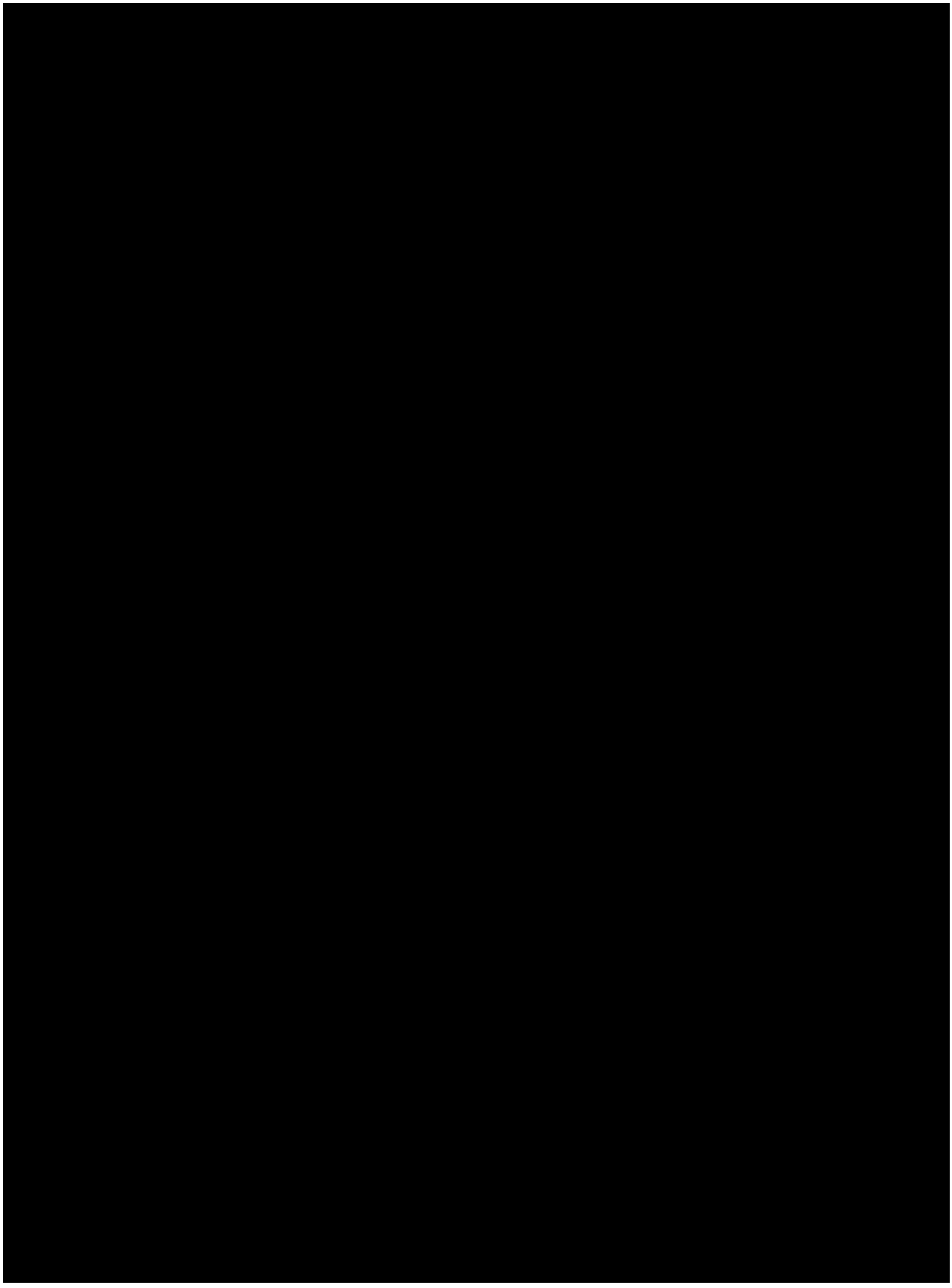


Figure 2: CyPass Applier, Model 231, with guidewire extended

[redacted]





4.2.3 ViscoPass Study (Initial Phase)

During the Dose Selection Phase of this study, 62 subjects were randomized using a 1:1:1 schedule to receive either CyPass Micro-Stent with 30 µl of adjunct Healon viscoelastic, CyPass Micro-Stent with 60 µl of adjunct Healon viscoelastic, or the CyPass Micro-Stent with no adjunct Healon viscoelastic.

With 6 months follow-up on all subjects, there was no difference in safety among the three arms, and the 60 µl arm had a comparable rate of AEs to either the Cypass only arm or the 30 µl arm. Also, there were no unanticipated or vision-threatening adverse events in either group. Additionally, there was a trend towards higher efficacy with the 60 µl arm compared to the other two arms for the primary and secondary efficacy outcomes.

Based on the results of the initial phase and considering the risk-benefit profile of each arm, the 60 µl arm was selected as the go-forward dose with recommended discontinuation of the 30 µl arm which had no appreciable benefit in either safety or efficacy.

5. STUDY DESIGN

This is a prospective, randomized, multi-cohort and multi-center investigation in which up to 150 subjects will be randomized to study treatment at up to 5 investigational sites. After successful completion of baseline assessments, eligible subjects will receive the CyPass Micro-Stent either with or without visco-assisted implantation and be followed for 12 months postoperatively. It is estimated that approximately 10% of those receiving the CyPass Micro-Stent may be lost to follow-up. Enrollment will be implemented in two phases, as follows:

Dose Selection Phase: During this phase, the first dose-selection cohort of 60 subjects will be randomized (1:1:1) to receive one of the following treatments:

- CyPass Micro-Stent with 30 µl adjunct Healon 5 viscoelastic, or
- CyPass Micro-Stent with 60 µl of adjunct Healon 5 viscoelastic, or
- CyPass Micro-Stent without adjunct viscoelastic.

After completion of at least 3 months follow-up on all subjects in the dose selection phase, an interim review of safety and efficacy data was performed to determine the optimum dose of adjunct viscoelastic for the study expansion phase.

Expansion Phase: After the dose selection phase, the study will be expanded to include a second cohort (Cohort 2) of up to 90 additional subjects who will be randomized 1:1 to either the CyPass Micro-Stent without adjunct viscoelastic or CyPass Micro-Stent with 60 µl of adjunct Healon 5 viscoelastic. This dose was selected based on previous phase results as discussed in Section 4.2.

5.1 Primary Endpoint

- Proportion of eyes with ≥ 20% decrease in IOP from baseline up to 12 months post-operatively without IOP lowering medications.

5.2 Secondary Endpoints

- Rate of intraoperative and post-operative device related ocular adverse events up to 12 months postoperatively
- Mean change in medicated IOP from baseline to 12 months postoperatively
- Proportion of eyes using ocular hypotensive medications at 12 months postoperatively
- Mean number of topical IOP lowering medications at 12 months postoperatively as compared with baseline.

6. STUDY POPULATION

6.1 Inclusion Criteria

Individuals will be assessed for study eligibility based on the criteria presented below. Unless specified otherwise, ocular criteria refer to the study eye only.

1. 21 years of age or older, male or female.
2. Able to understand study requirements, willing to follow study instructions, provide written informed consent, and comply with all study requirements, including required study follow-up visits.
3. Diagnosis of OAG, including pseudoexfoliation glaucoma and pigmentary glaucoma, which meets diagnostic criteria defined below:
   - Vertical cup-to-disc ratio (C:D) on fundoscopic exam of at least 0.6, or
   - Heidelberg Retinal Tomograph (HRT) of good quality demonstrating a Moorfield Regression Analysis that is "outside normal limits", or
   - Optical Coherence Tomography (OCT) demonstrating a thinness of the nerve fiber layer at the $p < 5\%$ level as defined by the instrument's built-in age-adjusted normative database.
   - Glaucoma Visual Field (VF) with a Mean Deviation (MD) < 0 dB
4. Baseline unmedicated IOP of 21 mmHg – 36 mmHg. *Note: Subjects who were using ocular hypotensive medication at the time of study enrollment must complete a required medication washout period prior to baseline IOP assessment as specified in Table 7.*
5. Gonioscopy confirming normal angle anatomy at site of implantation, and Shaffer grade of ≥ III in at least two quadrants, one of which must be the quadrant of the intended site of implantation.

6.2 Exclusion Criteria

Individuals with the following characteristics noted at or before the baseline examination will be excluded from the study. Unless specified otherwise, ocular criteria refer to the study eye only.

1. Advanced glaucoma evidenced by a C:D ratio > .95, or encroachment of field loss within the central 5 degrees as indicated by > 2 depressed points of 0.5% probability on the 24-2 SITA Standard Humphrey visual field or other standard automated perimetry test.
2. Aphakia.

3. Clinically significant ocular pathology other than glaucoma.
4. Any known ocular condition that may require intraocular intervention during the protocol-required follow-up period.
5. Diagnosis of acute angle closure, traumatic, congenital, malignant, uveitic or neovascular glaucoma.
6. Prior incisional glaucoma surgery.
7. Best corrected visual acuity (BCVA) of 20/200 (Snellen) or worse in the fellow eye.
8. Clinically significant ocular inflammation or infection within 30 days prior to the Baseline Visit.
9. 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.
10. Participation in any clinical trial within the past 30 calendar days prior to the Screening Visit.
11. Pregnant or nursing females.

Subjects who do not meet the inclusion/exclusion criteria specified will be exited from the study in accordance with Section 7.6 of the protocol.

7. STUDY PROCEDURES

7.1 Subject Enrollment

The Investigator will discuss study participation requirements, risks and benefits with patients that may be eligible for the study. The patient must sign a written Informed Consent Form (ICF) prior to the commencement of study-related procedures. Once the subject signs the ICF, he/she is considered to be enrolled in 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.

Only one eye per subject may be treated under the study protocol. If both eyes qualify for the study, the study investigator will choose which eye will be the study eye.

After the subject has successfully completed the preoperative screening exam, he/she will be instructed to discontinue use of ocular hypotensive medications in the study eye for the appropriate washout period listed in Table 7, *prior to* the Baseline Visit. If the subject experiences an IOP spike of > 36

mmHg, or requires the reintroduction of hypotensive medications or a surgical intervention during this period, the subject will be exited from the study.

Table 7

Ocular Hypotensive Medication Washout Requirements

Brand Name/Chemical Name	Minimum Washout Period
Carbonic Anhydrase Inhibitors	5 days
Alpha Adrenergic Agonists	14 days
Beta Blockers	28 days
Prostaglandin Analogs	28 days
Combined Medications	28 days
Other	Contact Sponsor

Subjects will be scheduled for a baseline examination within 45 days of screening, dependent on the required ocular hypotensive medication washout requirement after their screening examination. Subjects who are medication naïve at screening may have the screening and baseline testing performed on the same day. At the baseline examination, subjects will undergo further evaluation of eligibility. After successful completion of the baseline examination, the subject will be scheduled for surgery to receive the CyPass Micro-Stent.

It is recommended that the subject initiate the following perioperative medication regimen 2-3 days prior to the day of surgery:

- Topical NSAID (e.g., ketorolac) QID
- Topical antibiotic (4^{th} generation quinolone, e.g., gatifloxacin) QID
- Topical steroid (e.g., prednisolone acetate) QID

The fellow eye will be followed according to the standard of care. If a subject's study eye fails to qualify for surgery, the fellow eye may be considered for study enrollment once IOP in the study eye is considered to be controlled.

Ineligible subjects will be exited from the study and a study summary form completed. Subjects who are exited from the study at either the screening or baseline assessments will be replaced.

7.2 Subject Randomization

Subjects will be randomized to their assigned treatment group on the day of their surgical procedure. Randomization envelopes for each case will be provided for each study site.

During the Dose Selection Phase of the study, subjects will be randomized in Cohort 1 using a 1:1:1 schedule to receive either CyPass Micro-Stent with 30 µl of adjunct Healon viscoelastic, CyPass Micro-Stent with 60 µl of adjunct Healon viscoelastic, or the CyPass Micro-Stent with no adjunct Healon viscoelastic.

During the Expansion Phase of the study, subjects will be randomized in Cohort 2 using a 1:1 schedule to receive either CyPass Micro-Stent without adjunct Healon viscoelastic or the CyPass Micro-Stent with 60 µl of adjunct Healon 5 viscoelastic .

7.3 Surgical Procedure

The surgical procedure will be performed using intraocular microsurgical techniques and anesthesia per the investigator's standard procedure. The CyPass Micro-Stent will be implanted according to the Instructions for Use (IFU) for CyPass System 231.

Topical antibiotics and anti-inflammatory medication, as well as Apraclonidine, Brimonidine or other topical hypotensive agents may be administered at the conclusion of the procedure.
The topical antibiotic/steroid/NSAID medication regimen described in Table 8 below is recommended during the initial postoperative month.

Table 8

Medication Regimen

Time Period	Antibiotic	Steroid	NSAID
Surgery Day – Week 1	4th generation fluoroquinolone (e.g., moxifloxacin) QID	e.g., prednisolone acetate 1% QID	e.g., ketorolac QID
Week 2	N/A	e.g., prednisolone acetate 1% TID	e.g., ketorolac QID
Week 3	N/A	e.g., prednisolone acetate 1% BID	e.g., ketorolac QID
Week 4	N/A	e.g., prednisolone acetate 1% QD	N/A

Adjustments in the duration of postoperative medications may be necessary for subject safety.

7.4 Ocular Hypotensive Medication Re-Introduction

7.4.1 Medication Re-Introduction During 1st Postoperative Month

Ocular hypotensive therapy may be initiated within the first postoperative week if the subject's IOP > 21 mmHg. Additional IOP-lowering medication can be used with investigator discretion as necessary for IOP control.

7.4.2 Medication Re-Introduction After 1st Postoperative Month

Topical IOP lowering therapy may be initiated if the subject's IOP > 21 mmHg. Only 1 medication should be added at a visit. The preferred order of medication reintroduction should be as follows:

- Prostaglandin analogues
- Beta blockers
- Carbonic Anhydrase inhibitors
- Alpha agonists

Adjustments in IOP lowering therapy may be necessary for subject safety and should be based on investigator discretion.

7.5 Study Visits

Study subjects will participate in follow-up visits through 12 months postoperatively in accordance with Appendix 1 – Study Examinations and Procedures.

7.5.1 Unscheduled Visits

An unscheduled visit is any visit to the clinical site (other than those specified in the protocol), during which the subject has a complaint regarding the study eye or study eye treatment is required. No specific testing is required at unscheduled visits.

7.6 Subject Disposition

7.6.1 Terminated Subjects

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

- Screen failure
- AE(s)
- Administrative reasons (e.g., voluntary withdrawal, lost to follow-up)

Subjects who are terminated prior to surgery will not be followed beyond the date of termination unless the reason for termination in an IOP-related adverse event (AE). These subjects will be followed until resolution or stabilization of the AE. Subjects who are terminated prior to surgery due to a non-IOP-related AE will not be followed beyond the date of the AE report. Subjects who undergo surgery but do not receive the CyPass due to a surgical AE will be followed until resolution or stabilization of the AE. Subjects who receive the CyPass Micro-Stent but are terminated from the study should be followed for safety until the end of study period.

Study sites must make every attempt to follow-up on subjects who do not return for scheduled study examinations. If a subject is non-responsive to these follow-up attempts, he/she will be considered to be lost to follow-up. The sponsor should be notified promptly regarding subjects who are terminated prior to study completion.

Subjects terminated after implantation of the CyPass Micro-Stent will not be replaced.

7.6.2 Completed Subjects

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

8. STATISTICAL METHODS

8.1 Sample Size

The primary effectiveness endpoint is the outcome of ≥ 20% decrease in IOP from baseline without IOP lowering medications up to 12 months post-operatively (IOP response). The proportion of eyes meeting the effectiveness outcome, IOP response rate, will be assessed at 12 months. A sample of at least 101 eyes will be enrolled across the two groups (CyPass only control and CyPass + Healon 5 dose selected) with an estimated 86 eyes completing their month 12 visit. Assuming a 30% success rate for the control eyes and a 60% success rate for the visco-assisted eyes, 80% power can be achieved with 43 eyes per arm using a two-tailed alpha of 0.05.

8.3 Efficacy and Safety Analyses

The primary effectiveness endpoint, the achievement of a 20% decrease in IOP relative to baseline in the absence of IOP lowering medications will be summarized at each postoperative visit by the number available for analysis (N), the proportion meeting success criteria, and the 95% confidence interval (CI).

Secondary endpoints describing proportions meeting given criteria will be summarized at each postoperative visit by N, percentage and 95% CI. Continuous endpoints, IOP, mmHg decrease

in IOP and % decrease in IOP will be summarized by N, mean, standard deviation median, minimum and maximum. For continuous change measures, the 95% CI of that change will also be provided.

The safety profile of the CyPass device will be based on intraoperative and postoperative adverse event rates, slit lamp biomicroscopy and fundus examination. All subjects who undergo CyPass implantation surgery will be included in the safety analysis. The incidence of adverse events will be summarized by N, percentage, and CI.

[redacted]

9. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical sign occurring in a study subject, whether or not related to the CyPass Micro-Stent. All AEs in the study eye must be reported on the appropriate CRF. Each AE must be graded by degree of harm to the subject (note grading scale below), as well as by the relationship to study device or implantation procedure.

AEs should be graded 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

Ocular conditions or diseases that are chronic but stable and do not render the subject ineligible for the study should be recorded under the subject's ocular history. Changes in the chronic condition or disease consistent with natural progression are not considered AEs.

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

9.1 Intraoperative Adverse Events

- Lens touch
- Choroidal detachment
- Inadvertent perforation of sclera
- Hyphema, which obscures surgeon's view
- Inadvertent loss of vitreous
- Choroidal hemorrhage or effusion
- Significant iris injury or trauma
- Significant corneal damage
- Zonular dialysis

9.2 Postoperative Adverse Events

- Chronic pain in the study eye present at 3 months postoperatively or later
- Flat anterior chamber with lens/cornea touch
- Shallow chamber with peripheral iridocorneal apposition
- BCVA loss of 3 Snellen lines compared to baseline at 3 months postoperatively or later
- Hypotony (defined as IOP < 6 mmHg) at 1 month postoperatively or later
- Maculopathy
- Hypotonic maculopathy
- CyPass obstruction causing an untoward effect in the study eye
- CyPass malposition
- CyPass migration, causing an untoward effect in the study eye
- Wound dehiscence
- Persistent anterior chamber cell and flare requiring steroid treatment after 2 months postoperatively
- Endophthalmitis
- Cataract formation or progression outside of expected progression
- Persistent hyphema present at 1 week postoperatively or later
- Corneal opacification, or corneal decompensation
- Significant corneal edema
- Retinal complications (dialysis, flap tears, retinal detachment, or proliferative vitreoretinopathy)

- Choroidal hemorrhage or choroidal effusion, defined as a choroidal effusion or detachment with at least a partially hemorrhagic component that obstructs vision or causes pain (including both peripheral and "kissing" choroidal detachments) lasting longer than 1 month
- Significant elevation in IOP requiring non-medical intervention
- Other events resulting in unplanned ocular surgical reintervention (other than paracentesis to relieve pressure prior to 1 week postoperative or Nd:YAG laser procedure for treatment of posterior capsular opacification)
- Loss of eye
- Significant ptosis
- Atrophy/phthisis
- Significant foreign body sensation at or after 3 months postoperative
- Increase in C:D ratio of ≥ 0.3 units on slit lamp biomicroscopic examination
- Confirmed increase in visual field loss outside of expected progression

9.3 Serious Adverse Events

An AE should be classified as serious, regardless of relationship to the CyPass Micro-Stent if it:

- Led to death
- Led to a serious deterioration in health that:
  - Resulted in a life-threatening illness or injury, or
  - Resulted in a permanent impairment of a body structure or a body function, or
  - Required in-patient hospitalization or prolongation of existing hospitalization, or
  - Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

Serious Adverse Events (SAE) must be reported to Transcend Medical within 1 week of learning of the event.

9.4 Serious Adverse Device Effects

A serious adverse device effect (SADE) is an adverse event related to the use of the CyPass Micro-Stent that resulted in any of the consequences characteristic of a SAE. **SADEs must be reported to Transcend Medical within 24 hours of learning of the event.**

9.5 Device Deficiencies

A device deficiency is considered to be an inadequacy of the CyPass Micro-Stent System that is related to its identity, quality, durability, reliability, safety or performance (e.g., malfunction, misuse or user error, inadequate labeling). **Device deficiencies must be reported to Transcend Medical within 1 week of learning of the deficiency.**

To report any SAE, SADE or device deficiency, please contact:

Email: [redacted]
Phone: [redacted]
Fax: [redacted]

10. STUDY MONITORING PLAN

On-site monitoring visits will be performed periodically to assess the progress of the study and identify concerns related to adherence to the study protocol, EC review of the study and maintenance of study-related records and reports. Remote monitoring will be conducted and subject eligibility will be approved by the Sponsor prior to randomization.a.

11. DATA MANAGEMENT PLAN

Clinical study data will be documented on study-specific Case Report Forms (CRFs) and maintained in an electronic database, which has been established and validated for study use. The Sponsor will confirm data entry accuracy and issue data queries as necessary. Clinical study data will be maintained for the duration of the study until completion of the final clinical study report. Thereafter, the data will be archived by Sponsor.

12. ETHICAL AND REGULATORY CONSIDERATIONS

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP). These requirements are stated in global regulations as well as "Guidance for Good Clinical Practice", International Conference on Harmonization (ICH).
The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later amendments.

12.1 Sponsor Responsibilities

The Sponsor is responsible for the following activities with respect to this clinical investigation:

- Clinical quality assurance and quality control
- Clinical investigation planning and conduct, including: Selection of clinical personnel, Preparation of clinical investigation documents and materials, Clinical investigation conduct, Clinical investigation monitoring, Safety evaluation and reporting and Clinical investigation close-out

The Sponsor will maintain clinical study records throughout the study and for at least two years from the date on which the study was terminated or completed, and for providing access to these records for audit and inspection by regulatory authorities.

Additionally, the Sponsor is responsible for providing reports on the study progress and performance in accordance with applicable regulatory requirements.

12.2 Investigator Responsibilities

The principal investigator at each site is responsible for implementation and management of the day-to-day conduct of the clinical investigation as well as to confirm data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator must sign an Investigator Agreement acknowledging that he/she will comply with the protocol and other study obligations, including safety reporting. No changes in this protocol can be made without the Sponsor's written approval.

All Investigators must participate in a protocol review conducted by the Sponsor or the Sponsor's designated representative.

Investigators are responsible for maintaining clinical study records throughout the study and for at least two years from the date on which the study was terminated or completed, and for providing access to these records for audit and inspection by regulatory authorities.

12.3 Institutional Review

Before enrollment of any study subjects, the protocol and the subject ICF must be reviewed and approved by an EC that is operating in accordance with local procedures and regulatory requirements.

It is the responsibility of the Investigator to obtain and maintain approval for the study protocol and ICF, and to keep the EC informed of the occurrence of serious adverse events. It is also the Investigator's responsibility to maintain a file of all correspondence with the EC and to forward copies of that correspondence to the Sponsor or Sponsor's designated representative.

12.4 Subject Informed Consent and Confidentiality

Written informed consent is required prior to initiation of study-specific procedures or exams on study subjects. It is the responsibility of the Investigator to complete the informed consent process and to provide each subject with a copy of the fully executed ICF. The principal investigator and Sponsor (or designee) will use every effort will to ensure that subject names or other personal identifiers are not be used during the course of the study. All subject data will be kept in a secure location.

12.5 Device Accountability

Study devices will be shipped to the site or hand carried to the site by the Sponsor or Sponsor's designee. Study device shipment records should be verified by comparing the shipping receipt confirmation to devices received at the site. Study devices should be stored in a secure area to prevent unauthorized distribution.

The Investigator will be responsible for keeping current and accurate records of devices dispensed and implanted. After completion of study enrollment, all non-used study devices will be returned to the Sponsor or Sponsor's representative.

13. PUBLICATION POLICY

All publications and/or presentations concerning this study must be reviewed by the Sponsor prior to publication/presentation.

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