Multi-Center, Prospective, Randomized, Controlled Clinical Evaluation of the Safety and Effectiveness of the Sight Sciences VISCO™360 Viscosurgical System in Canaloplasty versus Selective Laser Trabeculoplasty in the Reduction of IOP in Primary Open Angle Glaucoma

Protocol SIGHTVISCO-001 [redacted]

February 1, 2017

COMPANY NAME AND ADDRESS

Sight Sciences, Inc.
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I have read and agree to follow the procedures as outlined in this protocol.

_____ _____

Signature of Investigator *Date*

CONFIDENTIALITY AGREEMENT

This protocol contains confidential proprietary information with respect to Sight Sciences, Inc. products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three (3) years after the completion of the study, or until said information shall become a matter of public knowledge or until a formal written agreement for that purpose has been entered into by the parties.

_____

Print Name of Investigator

_____ _____

Signature of Investigator *Date*

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MEDICAL MONITOR	[redacted]

STUDY SYNOPSIS

STUDY TITLE	A Multi-Center, Prospective, Randomized, Controlled Clinical Evaluation of the Safety and Effectiveness of the Sight Sciences VISCO™360 Viscosurgical System in Canaloplasty versus Selective Laser Trabeculoplasty in the Reduction of IOP in Primary Open Angle Glaucoma
INVESTIGATIONAL DEVICE	Sight Sciences VISCO™360 Viscosurgical System
CONTROL DEVICE	Selective Laser Trabeculoplasty (SLT)
STUDY OBJECTIVE	To establish the safety and effectiveness of the Sight Sciences VISCO™360 Viscosurgical System in support of the proposed Indications for Use Statement.
INDICATIONS FOR USE	The Sight Sciences VISCO™360 Viscosurgical System is a manually operated device for delivery of small amounts of viscoelastic fluid, for example Healon™ or HealonGV™ from Abbott Medical Optics (AMO), Amvisc™ from Bausch & Lomb, or PROVISC™ from Alcon, during ophthalmic surgery. The VISCO™360 Viscosurgical System is indicated for catheterization and transluminal viscodilation of Schlemm's canal (i.e. canaloplasty) to reduce intraocular pressure in adult, pseudophakic patients with open angle glaucoma.

STUDY DESIGN	This is a multicenter, prospective, single-masked, randomized, controlled trial. Two study groups will be included in the study. The treatment group consists of subjects who undergo canaloplasty with the VISCO™ 360 Viscosurgical System. The control group consists of subjects who undergo Selective Laser Trabeculoplasty (SLT). The clinical examinations and study visit schedules are included in Appendix 1. A total of approximately 298 subjects will be enrolled and randomized in a 1:1 ratio at up to 30 clinical sites. Only one eye from each eligible subject will be enrolled in the study. [redacted] • VISCO 360 Arm: 149 enrolled subjects • Control Arm: 149 enrolled subjects The study will consist of two phases. In the initial phase, 30 subjects will be enrolled and randomized at up to 5 of the 30 investigational sites. When the first 30 subjects randomized complete the 1-month follow-up examination, safety data will be submitted to the FDA to request approval for expansion to the full population in order to have 298 enrolled and treated subjects.
CLINICAL SITES	A maximum of 30 clinical sites will be selected. A minimum enrollment of ten investigational device subjects per investigator should be sought. No investigator should enroll more than 25% of the total number of investigational device or control subjects. For centers with more than one investigator, the center's total enrollment (investigational or control arm) should not exceed 33% of the total. Investigational sites for the clinical study will be selected with the goal of obtaining an appropriate balance of gender, minority, and age during the study.
ELIGIBILITY CRITERIA	**Inclusion Criteria** (only one eye of each subject is eligible and all criteria apply to study eye only unless otherwise indicated): 1. Male or female subjects, 22 years or older. 2. Pseudophakic with Posterior Chamber IOL (PCIOL) 3. Subjects diagnosed with mild to moderate primary open angle glaucoma (POAG). The diagnosis of POAG must include evidence of: o Glaucomatous optic nerve damage as evidenced by any of the following optic disc or retinal nerve fiber layer structural abnormalities documented with stereo disc photos: ▪ Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles ▪ Localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles ▪ Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue ▪ Disc rim or peripapillary retinal nerve fiber layer hemorrhages

	And/Or o Visual field defect consistent with glaucomatous optic nerve damage (substantiated with the Humphrey automated perimeter using the SITA Standard 24-2 testing algorithm). Mean deviation (MD) score must be between -3dB and -12dB corresponding to Mild/Moderate disease (Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol 2006; 141:24-30.) At least one of the following two findings: (1) On pattern deviation (PD), there exists a cluster of 3 or more points in an expected location of the visual field depressed below the 5% level, at least 1 of which is depressed below the 1% level; (2) Glaucoma hemi-field test "outside normal limits." 4. Intraocular pressure ≥ 18.0 mmHg and ≤30.0 mmHg and not at the patient's target pressure while on 1-3 topical ocular medications or while not on topical ocular medication due to intolerance of medication or history of poor compliance (Screening Visit). Combination glaucoma medications that consist of two or more glaucoma drugs will have each glaucoma drug component counted as a separate drug. 5. At the Baseline Visit, an unmedicated IOP ≥ 21.0 mmHg and ≤ 36.0 mmHg and ≥ 3.0 mmHg higher than the medicated IOP measured at the Screening Visit 6. Shaffer grade of ≥ III in all four quadrants 7. Subjects able and willing to comply with the protocol, including randomization assignment and all follow-up visits through 24 months. 8. Subject understands and signs the informed consent. **Exclusion Criteria** (All criteria apply to the study eye unless otherwise noted and both eyes of a single subject need not be eligible): 1. Phakia or aphakia 2. Posterior Capsular Opacification graded as moderate or severe using the sample images provided in Appendix 1. In this case, a laser capsulotomy can be performed and the subject screened again a minimum of two weeks following the capsulotomy. 3. Presence of Anterior Chamber IOL (ACIOL) 4. History of complicated cataract surgery (e.g. vitreous loss, sutured IOL, decentered IOL, etc.) 5. Pre-existing IOL instability 6. Diagnosis of acute angle closure, traumatic, congenital, malignant, uveitic, pseudoexfoliative, pigmentary or neovascular glaucoma 7. Inability to properly visualize angle (due to corneal scar, edema, etc.) 8. Abnormal angle anatomy as determined by gonioscopy (e.g. peripheral anterior synechiae, rubeosis or other angle abnormalities)

	9. Conditions associated with elevated episcleral venous pressure such as active thyroid orbitopathy, cavernous sinus fistula, Sturge-Weber syndrome, orbital tumors, orbital congestive disease. 10. The subject would be at significant risk by washout of ocular hypotensive medication including any of the following: o Unmedicated IOP after washout period is expected to exceed upper limit of 36.0 mmHg at Baseline visit o Presence of afferent pupillary defect in either eye o C:D ratio ≥ 0.9 in either eye o Requiring oral medications (e.g., acetazolamide) for IOP control in either eye o Evidence of advanced glaucoma in either eye by 24-2 SITA Standard Humphrey visual field defined as mean deviation (MD) of -12.00 or worse and at least one of the following: (a) On PD plot, greater than or equal to 75% of points depressed below the 5% level and greater than or equal to 50% of points depressed below 1% level; or (b) At least 50% of points (i.e., 2 or more) within central 5 degrees with sensitivity of < 0dB on the dB plot; or (c) Points within the central 5 degrees of fixation with sensitivity < 15dB in both hemifields on the dB plot. o Visual field defects threatening fixation in either eye defined as any (1 or more) point(s) within the central 5° depressed below the 5th percentile on PD plot unless this/these points are >25 dB on Threshold Values (decibel) plot. 11. Subjects with Snellen best-corrected visual acuity worse than 20/80 in either eye. 12. At Baseline visit, subject has not completed appropriate medication washout, if applicable 13. Inability to complete a reliable 24-2 SITA Standard Humphrey visual field at screening (fixation losses, false positive errors and false negative errors should not be greater than 33%). *A visual field done within 90 days prior to the subject informed consent date and in accordance with the 24-2 SITA Standard requirements can be used for the screening evaluation.* 14. Use of more than 3 ocular hypotensive medications (combination medications count as 2 medications) 15. Use of oral hypotensive medication treatment for glaucoma 16. Previous glaucoma procedure with or without an implantable glaucoma device (including incisional surgery, ALT, iridectomy/iridotomy, etc.). ***Subjects with one prior 180 degree SLT application or one prior 360 degree SLT application (>3 months prior to screening) or prior ECP (performed > 12 months prior to screening) can be enrolled.*** 17. Clinically significant sequelae from trauma (e.g., chemical burns, blunt trauma, etc.) 18. History of elevated IOP due to steroid response 19. Use of systemic medications (either current, within 30 calendar days of screening exam, or anticipated) that may cause an increase in IOP, (e.g., systemic steroids including inhaled steroids used on a regular basis) 20. Ocular pathology or medical condition for which, in the investigator's judgment, the following factors would either place the subject at increased risk of complications or contraindicate surgery or interfere with

	compliance to elements of the study protocol (e.g., ophthalmic examinations, follow-up visits): a) inability to reliably complete visual field testing over the course of the study, b) uncontrolled systemic disease (e.g. diabetes, hypertension) that could compromise their participation in the study, c) disorders that pose a fall risk, as well as compromise ability to take a visual field exam and take glaucoma medications (e.g., Parkinson's disease), d) inability to discontinue use of blood thinners in accordance with surgeon's standard pre-operative and postoperative instructions, e) immunodeficiency concerns, f) other clinically significant ocular pathology other than glaucoma. 21. Proliferative diabetic retinopathy 22. Previous surgery for retinal detachment 23. Central corneal thickness that is less than 450 microns or greater than 620 microns. 24. Clinically significant corneal dystrophy (e.g., bullous keratopathy, guttata, etc.) 25. Previous corneal surgery 26. Wet age-related macular degeneration 27. Clinically significant ocular inflammation or infection ≤ 30 days prior to screening. 28. Participation in any clinical trial ≤ 30 days prior to screening. 29. Women of childbearing potential if they are currently pregnant or intend to become pregnant during the study period; are breast-feeding; or are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study. (A negative serum pregnancy test must be verified for females of child bearing potential). All women are considered to be of childbearing potential unless: A. Postmenopausal for at least 1 year OR B. Surgically sterile
STUDY DURATION	The primary safety and effectiveness endpoints will be evaluated when each study subject has a minimum of 12 months of post- follow-up data. All subjects will be followed through the 24-month time point.
SCHEDULE OF VISITS	1 day, 1 week, and 1, 3, 6, 12, 18, and 24 months

STUDY PROCEDURES	**Diurnal IOP:** Each time IOP is measured, the physician or technician is to utilize a Goldmann tonometer; however, the individual operating the tonometer should not view the dial during the measurement and another individual who is masked to the treatment should read the measurement and then record the measurement to minimize observer bias. Each time IOP is measured, two measurements should be taken and the mean recorded on the case report form unless they differ by more than 2mmHg in which case a third measurement is taken and the median value is recorded. All measurements must be recorded within the source documents. In order to determine the mean diurnal intraocular pressure (IOP) measurements at baseline and 12 months, values should be taken at 9:00AM ±1.5 hours, 12:00PM ± 1 hour, and 4:00PM ± 2 hours. The three IOP measurements should then be averaged to determine the mean diurnal IOP. **Washout** All subjects on ocular hypotensive medication(s) at Screening and Month 12 will be instructed to undergo a washout prior to the Baseline/Month 12 postoperative visit. If a subject cannot be washed out of their ocular hypotensive medications, the medical monitor will review the subject records and the decision in a masked fashion.
STUDY ENDPOINTS	**Effectiveness** The primary effectiveness endpoint is change in mean diurnal IOP from baseline at 12 months compared between the VISCO360 group and the control group. The secondary effectiveness endpoint is the proportion of subjects achieving a ≥ 20% reduction in mean diurnal IOP from baseline at 12 months compared between the VISCO360 group and the control group. Subjects who meet any of the pre-defined criteria in the protocol will be imputed as failures in the responder analysis at 12 months. **Safety** • Best corrected visual acuity (BCVA) changes from baseline; • Findings from pachymetry, slit lamp, fundus and gonioscopic examinations; • Rates of ocular adverse events (intraoperative, postoperative); [redacted]

	[redacted]

SAMPLE SIZE AND STATISTICAL ANALYSIS	The statistical analysis plan has been detailed in a separate document. The sample size for the primary effectiveness endpoint and the corresponding statistical hypotheses is based on the following assumptions and criteria. • The standard deviation of change in mean diurnal IOP from baseline at 12 months is assumed to be 5.0 mmHg. Per Seymenoglu[1], the mean and standard deviation (SD) of the change in IOP from baseline to 12 months was 5.5 mmHg ± 3.8 mmHg for the pseudophakic eyes with SLT, without additional medications, without SLT retreatments, and without any glaucoma-related secondary surgical intervention. Since the study will study the change in the mean diurnal IOP from baseline after washout to 12 months after washout, the SD of the endpoint is expected to be larger than the published SD of 3.8 mmHg. It is assumed an SD of 5 mmHg for the study. • Significance level is 0.025 (one-sided) and statistical power is 90% at a true mean difference of 2 mmHg. • Two-sample *t*-test will be used. • A yearly dropout rate of 10% is considered. • The randomization ratio for the study is 1:1. Based on the criteria above, the 12-month sample size for the primary effectiveness endpoint and corresponding statistical hypotheses are 133 VISCO 360 and 133 control subjects at 12 months. With the yearly dropout rate of 10%, approximately 296 subjects (148 VISCO 360 and 148 controls) should be randomized. [redacted]

[1] Seymenoğlu G, Baser EF. Efficacy of Selective Laser Trabeculoplasty in Phakic and Pseduphakic Eyes. J. Glaucoma 2015;24:105–110.

	
SCHEDULE OF VISITS AND LIST OF EVALUATIONS	• Screening (Day -45 TO -2) • Baseline (Day -15 TO 0 after completion of medication washout) • Surgery/SLT Procedure (Day 0) • 1 Day Postop (Day 1) • 1 Week Postop (Day 5-9) • 1 Month Postop (Day 21-35) • 3 Months Postop (Day 70-98) • 6 Months Postop (Day 150 –210) • 12 Months Postop (Day 330 – 420) • 12 Month Washout (Day 330 – 420, after completion of medication washout)[2] • 18 Months Postop (Day 510 – 600) • 24 Months Postop (Day 690 – 780)

1.0 STUDY OBJECTIVE

To establish the safety and effectiveness of the Sight Sciences VISCO™360 Viscosurgical System in support of the proposed Indications for Use Statement.

2.0 STUDY DESIGN

This is a multi-center, prospective, single-masked, randomized, and controlled study. Subjects who meet the study enrollment criteria will be randomized to viscocanaloplasty with the VISCO™360 Viscosurgical System or Selective Laser Trabeculoplasty (SLT).

A total of approximately 298 subjects will be enrolled and randomized in a 1:1 ratio at up to 30 clinical sites. Only one eye from each eligible subject will be enrolled in the study. If both eyes are eligible, the right eye will be selected for the study.

- VISCO 360 Arm: 149 enrolled subjects
- Control Arm: 149 enrolled subjects

Anticipating a 40% screening failure rate (including baseline IOP failure), up to 497 subjects will undergo screening and baseline exams in order to have at least 298 randomized subjects, and have at least 134 randomized subjects per study group reach the 12-month visit, assuming an annual drop-out rate of 10%. In order to minimize the number of subjects with out-of-window visits at 12 months and to perform the specified washout of any ocular hypotensive medications for subjects, the investigational sites will be reminded of subjects with upcoming 12-month visits.

See separate Statistical Analysis Plan for more information related to sample size calculation.

A washout of ocular hypotensive medications, if necessary, will be performed at baseline and at 12 months. The primary effectiveness endpoints will be evaluated at 12 months and all study subjects will be followed for 24 months.

A minimum enrollment of ten investigational device subjects per investigator should be sought. No investigator should enroll more than 25% of the total number of investigational device or control subjects. For centers with more than one investigator, the center's total enrollment (investigational or control arm) should not exceed 33% of the total.

Investigational sites for the clinical study will be selected with the goal of obtaining an appropriate balance of gender, minority, and age during the study.

The study will consist of two phases. In the initial phase, 30 subjects will be enrolled and randomized at up to 5 of the 30 investigational sites. When the first 30 subjects randomized complete the 1-month follow-up examination, safety data will be submitted to the FDA to request approval for expansion to the full study population in order to have 298 enrolled and randomized subjects.

3.0 INTRODUCTION AND BACKGROUND

Glaucoma is a term describing a group of ocular disorders with multi-factorial etiology united by a clinically characteristic intraocular pressure-associated optic neuropathy. Glaucomatous optic neuropathy can lead to irreversible, progressive visual field loss often resulting in blindness. It is often associated with increased intraocular pressure in the eye where there is decreased facility of outflow of the fluid in the eye (aqueous humor). Glaucoma has been called the "silent thief of sight" because the loss of vision often occurs gradually, painlessly, and asymptomatically over a long period of time, and symptoms become manifest only when the disease is quite advanced. Once lost, vision cannot be recovered, so treatment is aimed at preventing further loss. Worldwide, glaucoma is the second-leading cause of blindness after cataracts and it is the number one cause of irreversible blindness. It is also a particularly severe cause of blindness among those of African extraction. Glaucoma affects one in 200 people aged fifty and younger and one in 10 over the age of eighty. The disease affects 60-80 Million people worldwide. If the condition is detected early enough, it is often possible to arrest the development or slow the progression with medical and surgical means.

Optic nerve damage in glaucoma involves loss of retinal ganglion cells in a characteristic pattern. The many different subtypes of glaucoma can all be considered to be a type of optic neuropathy. Raised intraocular pressure (typically above 21 mmHg) is the most important and only currently known modifiable risk factor for glaucoma. However, some may have high eye pressure for years and never develop damage, while others can develop nerve damage at a relatively low pressure. Untreated glaucoma can lead to permanent damage of the optic nerve and resultant visual field loss, which over time can progress to blindness.

Glaucoma can generally be divided into two broad categories, "open-angle" and "closed-angle" (or "angle closure") glaucoma. The anterior chamber angle refers to the angle formed between the anterior surface of the iris and posterior surface of the cornea. At the vertex of this angle resides the trabecular meshwork through which fluid must flow to escape the eye and ultimately enter the systemic venous circulation. Closed-angle glaucoma can appear suddenly and is often painful; visual loss can progress quickly, but the discomfort often leads patients to seek medical attention to expedite treatment. Chronic, open-angle glaucoma tends to progress at a slower rate and patients may not notice they have lost vision until the disease has progressed significantly.

3.1 AQUEOUS HUMOR OUTFLOW PATHWAY

Aqueous humor circulation through the anterior segment of the eye represents one of the many cardiac circulatory loops that also include the various arteriovenous, lymphatic, and cerebrospinal fluid circulations. Each of these circulatory loops is driven down a continuous pressure gradient initially set up by the heart. Aqueous humor is formed by the ciliary processes, passes from the posterior chamber to the anterior chamber through the pupil, and exits the eye at the anterior chamber angle.

Aqueous returns to the venous system primarily by means of the conventional or trabeculocanalicular pathway (83-96% of flow). The pathway is through the trabecular meshwork into Schlemm's canal (hence the "trabeculocanalicular" pathway). Aqueous collector channels connect the lumen of Schlemm's canal to the episcleral veins, completing the circulatory pathway for aqueous return to the heart.

Aqueous humor also returns to the heart by a secondary pathway known as the uveoscleral or unconventional route. The uveoscleral route accounts for from 5 to 15% of flow. Extracanalicular aqueous flow is through the anterior ciliary muscle and iris stroma to reach the supraciliary and suprachoroidal spaces. From these spaces the fluid passes through the sclera and the loose connective tissue around the penetrating nerves and vessels.

3.2 TRABECULOCANALICULAR OUTFLOW PATHWAY PHYSIOLOGY AND RESISTANCE

The trabecular meshwork is an area of tissue in the eye located around the base of the cornea, near the ciliary body, and allows for drainage of the aqueous humor from the anterior chamber of the eye (the fluid filled space bound anteriorly by the corneal endothelium and posteriorly by the iris plane). The meshwork tissue is spongy, porous, and lined by trabeculocytes; it allows fluid to drain into a modified vascular sinus called Schlemm's canal that then drains into collector channels which themselves drain into the systemic circulation.

The meshwork is divided up into three parts, with characteristically different ultrastructures:

1. Inner uveal meshwork – Closest to the anterior chamber angle, contains thin cord-like trabeculae, orientated predominantly in a radial fashion, enclosing trabeculae spaces larger than the corneoscleral meshwork.

2. Corneoscleral meshwork – Contains a large amount of elastin, arranged as a series of thin, flat, perforated sheets arranged in a laminar pattern; considered the ciliary muscle tendon.

3. Juxtacanalicular tissue – Lies immediately adjacent to Schlemm's canal, composed of connective tissue ground substance full of glycoaminoglycans and glycoproteins. This thin strip of tissue is covered by a monolayer of endothelial cells.

Schlemm's canal is a modified wall of a vessel. In other vessels such as arteries, pressure gradients are higher in the vessel lumen. With the canal, in contrast, pressures are higher external to the lumen of Schlemm's canal. Intravascular fluid moves from the higher pressure in the lumen of vessels across vessel walls to the lower pressure in adjacent tissues as a response to the hydrostatic pressure gradient. Again, in contrast, aqueous humor flows from the anterior chamber, across the modified vascular wall represented by the trabecular meshwork, into the lower pressure vascular lumen of Schlemm's canal. A series of adaptations is required as a result of the pressure gradient and fluid flow reversals. These adaptations are reflected in the unique tissue anatomy, geometry and responses to pressure in the wall of Schlemm's canal that differ from those of the walls of other vessels.

Schlemm's canal is a vascular sinus with a lumen that is circumferential around the entire anterior chamber angle. The lumen has a flattened elliptical cross-section with a circumference of approximately 36 mm. As the lining wall of a vessel, Schlemm's canal endothelium has properties of a vascular endothelium. The canal is surrounded by sclera, trabecular meshwork, and the scleral spur. Generally, Schlemm's canal has a lumen that is 190-370 microns in length in the radial plane. In hypotony, the shape varies, but when Schlemm's canal shape is triangular, the lumen typically measures approximately 50 microns at its posterior base and narrows to about 5-10 microns at its apex. However, the diameter of the canal lumen is IOP dependent and the space can be absent at high pressures or very large at low pressures. Contrary to popular thought, the canal may sometimes be compartmentalized with septae or walls that may limit continuous circumferential flow.

Schlemm's canal is drained by a series of collector channels that in turn drain into a complex system of intrascleral, episcleral, and subconjunctival venous plexus. The collector channels arise from the outer wall of Schlemm's canal at irregular intervals (0.3- 2.8 mm) that average 1.2 per mm creating a total of 20-30 collector channels. At the origin of some collector channels, openings are observed that are associated with septa. Septa at collector channel ostia limit or prevent trabecular tissue from completely occluding the opening. A few (4-6) direct collector channels (approximately 70 micron diameter) proceed directly from Schlemm's canal through the sclera thus communicating directly with aqueous veins on the surface of the eye. Indirect collector channels are smaller (approximately 50 micron diameter), more numerous (15-20) and enter into the intrascleral drainage network. A few (4-6) intermediate types are present.

3.3 OUTFLOW RESISTANCE

Raised intraocular pressure (IOP) can theoretically result from three causes: increased aqueous production, elevated systemic venous pressure, or increased aqueous outflow resistance (reduced aqueous outflow). There is a great deal of experimental evidence suggesting that in a majority of patients, raised IOP results from an abnormality of the resistance characteristics of the outflow system. Investigators have proposed two different leading models of the exact resistance location and mechanism, but both are located within the overall trabeculocanalicular tissue.

The first model envisions the main resistance localized to the juxtacanalicular space. The juxtacanalicular space acts as a syncytium of extracellular matrix material and elastic-like fiber network that attaches to Schlemm's canal endothelium. The syncytium must provide a sufficiently stable geometry so that the extracellular matrix material can act as a passive filter regulating resistance. After passing through the juxtacanalicular resistance, aqueous passes through low-resistance pores in Schlemm's canal endothelium.

The second model places the initial resistance to IOP-generated forces at Schlemm's canal endothelium. The model necessitates redistribution of IOP-induced resistive forces at Schlemm's canal endothelium to structural elements throughout a tensionally integrated trabecular meshwork. The force redistribution takes place via cytoplasmic process attachments to Schlemm's canal endothelium. A second component of the Schlemm's canal endothelium/trabecular meshwork resistance model is pressure-induced distention of Schlemm's

canal inner wall: such a distention leads to apposition between Schlemm's canal walls. Schlemm's canal wall apposition thus becomes a resistance element integral to the model.

Regardless of which model of the resistance location and mechanism one supports, it is reasonable to conclude that the greatest resistance to aqueous outflow occurs in the trabecular meshwork, juxtacanalicular tissue, and/or Schlemm's canal.

Technologies that are designed to target and disrupt (ablate, cut, stretch, dilate, stent, bypass) any or all of these tissues have been developed that have successfully demonstrated varying degrees of IOP-lowering. Among the commercially available medical device technologies that are sold globally today include the iStent™ Trabecular Microbypass Stent (Glaukos), the iTrack™ Canaloplasty Microcatheter (Ellex iScience), the Trabectome™ Trabeculotomy System (NeoMedix), the Viscocanalostomy Probe (Rumex International), and the Harms™ Trabeculotomy Probe (Katena Eye Instruments).

3.4 SELECTIVE LASER TRABECULOPLASTY

Laser trabeculoplasty (LTP) has been used as an initial, adjunct, or replacement therapy in the lowering of IOP in patients with open angle glaucoma (OAG). Originally, LTP was performed with an argon laser. Argon laser trabeculoplasty or ALT was shown in prospective studies to be a relatively safe and effective procedure. The Glaucoma Laser Trial showed that in patients with newly diagnosed OAG, ALT was at least as effective as initial treatment with timolol maleate 0.5%, even after 7 years.

In 2001, the FDA approved selective laser trabeculoplasty (SLT) for the reduction of IOP. SLT uses a 532nm, frequency doubled, Q-switched Nd. YAG laser, and this results in a selective absorption by pigmented cells thereby sparing adjacent cells and tissue from thermal injury and producing less thermal damage to the trabecular meshwork compared with ALT. While SLT was considered a secondary treatment in OAG, some studies have proven its effectiveness as a primary treatment of OAG prior to medical therapy.[2] Non-comparative trials have shown IOP reduction from untreated baseline sustained for at least 3 years. Other studies have shown that following treatment with SLT, medication use could be reduced, and SLT's comparable effectiveness to prostaglandin analog medication.[3, 4]

3.5 RATIONALE FOR THE STUDY

The Sight Sciences VISCO™360 is a 510(k) cleared manual surgical tool for delivery of small amounts of viscoelastic fluid into the eye including the anterior segment (K132494 and K143205). Among the anatomical spaces the VISCO™360 can access within the anterior segment is Schlemm's Canal with the goal of reducing intraocular pressure through catheterization and transluminal viscodilation of the canal, i.e. "canaloplasty". Therefore, Sight

Sciences will conduct a prospective, multicenter trial to establish the safety and effectiveness of the VISCO™360 Viscosurgical System for the catheterization and transluminal viscodilation of Schlemm's canal to reduce intraocular pressure in adult, pseudophakic patients with open angle glaucoma.

The possible benefits were weighed against the possible risks for the procedure and the device used in the VISCO™360 canaloplasty procedure. Adverse device effects due to mechanical issues, biological hazards, and user interface hazards were studied carefully and are described in detail in the Failure Mode and Effects Analysis (FMEA) documents.

Design risks related to biocompatibility, sterility, mechanical integrity, and cleaning during manufacturing were mitigated by complying with international standards and manufacturing practices.

The VISCO™360 Viscosurgical System procedure will be performed with the aim to reduce intraocular pressure (IOP) in a safe, reproducible, and minimally invasive manner. Some anticipated key benefits of IOP reduction include preservation of functional vision and a reduction in medication use.

Ab interno canaloplasty with VISCO™360 Viscosurgical System is expected to provide equivalent or better IOP reduction as compared to an *ab externo* approach while avoiding some of the complications associated with an *ab externo* approach (e.g. inadvertent bleb, suture extrusion through the TM, etc.). Following trabeculectomy, serious complications may develop in the perioperative and postoperative period.[5,6,7] Risks include hypotony [8,9] hypotony maculopathy [10,11] bleb leaks, dysesthesias [12,13] and endophthalmitis [8,14,15] and these occur with

greater frequency when compared to glaucoma surgeries that do not involve subconjunctival filtering of aqueous and the formation of a filtering bleb. [16,17,18,19,20,21,22,23,24]

Similarly, tube-shunt surgeries have serious long-term complications including hypotony, diplopia and tube erosion .[8,25] *Ab interno* surgeries utilize the intrinsic outflow paths of the eye and avoid the risks associated with subconjunctival hardware in tube shunt surgeries and with subconjunctival blebs. Specifically, canal based surgeries are bleb-less and have thus avoided many of the complications associated with blebs. [26,27,28,29,30,31,32]

[redacted]

The goal of glaucoma treatment is to prevent visual field loss and concomitant visual disability and reduction in quality of life. Because POAG may be present in a patient without a detectable visual field defect, the American Academy of Ophthalmology Preferred Practice Pattern (PPP) [33] defined 'mild' glaucoma as "optic nerve abnormalities consistent with glaucoma….and a normal visual field test with standard automated perimetry" and structural evidence of optic nerve damage may serve as a basis for diagnosis with or without visual field abnormality.

Early studies by Quigley and others showed that more than 50% of the nerve fibers may be lost by the time reproducible early visual field defects are found. In addition, only 10% of nerve fibers may remain by the time patients have severe visual field deficits.[34,35,36] These initial studies used kinetic perimetry. Subsequently, Quigley found that automated perimetry had some advantages and was able to detect visual field loss after 20-40% of optic nerve axon loss.[37] Thus, it can be reasoned that significant optic nerve loss can often precede any detectable visual field changes and the goal of earlier IOP control is to slow visual field loss and prevent visual disability such that bleb-free glaucoma surgery need not be reserved for patients with more advanced glaucoma (i.e. significant, irreversible optic nerve damage).

4.0 DEVICE DESCRIPTION

This study evaluates the Sight Sciences VISCO™360 Viscosurgical System in Canaloplasty. There is only one device model in the clinical study.

The VISCO™360 Viscosurgical System is a non-implantable, sterile, manual, single use, 510(k)-cleared surgical ophthalmic instrument manufactured by Sight Sciences, Inc.

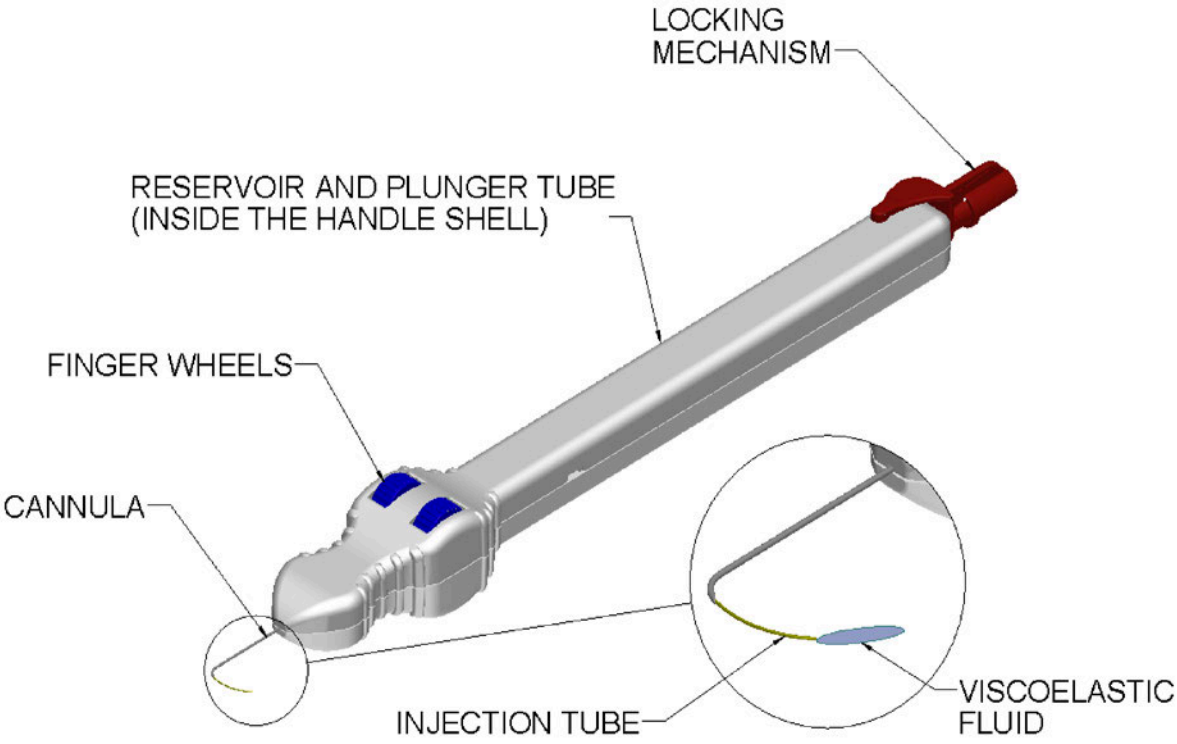
VISCO™360 dispenses fluid on the principle of exchanging volumes much like a syringe. The handheld instrument includes a cannula, microcatheter, internal reservoir, plunger tube and finger wheels. Finger wheels on both sides of the instrument handle control microcatheter advancement and retraction to facilitate the canaloplasty procedure in either eye using either hand. The finger wheels advance the plunger tube into the viscoelastic fluid reservoir thereby dispensing viscoelastic fluid.

[redacted]

The Sight Sciences VISCO™360 is used for delivery of small amounts of viscoelastic fluid into the eye including the anterior segment. The VISCO™360 components responsible for the fluid dispensing are the following:

- The reservoir within the handle is analogous to a syringe plunger. Prior to use, the viscoelastic fluid is loaded into the reservoir.
- The plunger tube is connected to the injection tube and it communicates with the reservoir. During use the plunger tube acts like the graduated cylinder.
- The injection tube, initially located within the cannula, advances and retracts from the device to dispense fluid. The injection tube is analogous to a syringe dispensing-tip.
- The user interfaces with the device by using the finger wheels. This action is analogous to moving the dispensing tip to the desired location and depressing the plunger handle, see **Figure 1**.

FIGURE 1: THE SIGHT SCIENCES VISCO™360 VISCOSURGICAL SYSTEM



To operate the device and dispense fluid, first the entire device including the reservoir, plunger tube and injection tube are flushed with viscoelastic fluid until fluid is visualized at the cannula tip. Next, the device is placed within the eye and using the finger wheel, the injection tube is advanced from the cannula to the desired location for fluid dispensing. Advancing the injection tube also moves the reservoir and plunger tube forward or distal within the handle. Finally, the injection tube is retracted into the cannula and fluid is dispensed. Retracting the injection tube displaces the plunger tube into the reservoir to exchange volume and dispense fluid. Since the injection tube and plunger tube are connected, the fluid flows from the reservoir through the plunger tube and out of the injection tube.

5.0 PRIOR PRE-CLINICAL AND CLINICAL TESTING

The VISCO360 injector has been subjected to a comprehensive battery of nonclinical laboratory studies reviewed by FDA to support 510(k) clearance:

- Biocompatibility
- Sterilization
- Shelf-Life
- Packaging Integrity
- Mechanical testing

Additionally, a review of the clinical literature was performed which described the outcomes following *ab externo* viscocanalostomy and *ab externo* canaloplasty for the reduction of IOP. Viscocanalostomy involves the viscodilation of only 60-90 degrees of Schlemm's canal using a rigid, stainless steel injection needle. Canaloplasty, used to dilate all 360 degrees of Schlemm's Canal, is the evolution of viscocanalostomy using catheters which are flexible and are able to transluminally circumnavigate and viscodilate up to all 360 degrees of Schlemm's canal. These surgical approaches have been performed over the past two decades and found to have a good safety and effectiveness profile. The clinical experience with both procedures is described below.

5.1 VISCOCANALOSTOMY

Ab externo viscocanalostomy unroofs and dilates Schlemm's canal without penetrating the trabecular meshwork or anterior chamber. It was pioneered by Dr. Robert Stegmann in the 1990's. In this procedure, a high-viscosity viscoelastic solution (sodium hyaluronate) is used to dilate a 60-90 degree section of Schlemm's canal and the trabecular meshwork. Viscocanalostomy is effective at lowering IOP and it avoids bleb-related complications. Like other *ab externo* approaches, however, it does not spare conjunctiva, sclera, or limbus.

Chai and Loon performed a meta-analysis comparing the safety and efficacy of viscocanalostomy with the gold standard of trabeculectomy.[38] Ten randomized controlled trials comprised of a total of 458 eyes of 397 subjects with medically uncontrolled glaucoma were included in the analysis. The number of eyes in each study ranged from 20 to 60, with follow-up ranging from 6 months to 4 years. The majority of eyes (81%) had POAG, while 16.4% had secondary open angle glaucoma (OAG), and 1.7% had primary angle closure glaucoma. The difference in intraocular pressure (IOP) between the treatments was 2.25 mm Hg at 6 months, 3.64 mm Hg at 12 months, and 3.42 mm Hg at 24 months. Viscocanalostomy had significantly fewer postoperative events, such as hypotony or shallow anterior chamber, compared with trabeculectomy.

A study by Gilmour and colleagues, included in the previously noted meta-analysis, consisted of 50 eyes of 43 individuals with open angle glaucoma randomized to have either a viscocanalostomy (25 eyes) or trabeculectomy (25 eyes) and prospectively followed at regular intervals for up to 60 months.[39] A successful outcome was defined as IOP less than 18 mm Hg with no medications; a qualified success was defined as IOP less than 18 mm Hg with or without topical treatment. One person from each group was lost to follow-up. At baseline, subjects had a mean IOP of 25 mm Hg and were using an average of 1.4 medications. At mean follow-up of 40 months (range, 6 to 60 months), 10 subjects (42%) in the trabeculectomy group had achieved success compared to 5 (21%) in the viscocanalostomy group. 19 individuals (79%) in both groups achieved qualified success. The trabeculectomy group required less additional topical treatment (50% vs. 83%) to achieve qualified success. There were more early postoperative complications in the trabeculectomy group including hypotony, wound leak, and choroidal detachment. The authors concluded that viscocanalostomy is effective at lowering IOP and has a very good safety profile. The meta-analysis demonstrated that both procedures were effective in lowering pressure. The trabeculectomy cohort experienced better pressure-lowering outcomes and viscocanalostomy cohort experienced a better safety profile.

David and colleagues in 2008 published a prospective, nonrandomized case series of 46 eyes (46 patients) with medically uncontrolled primary and secondary open angle glaucoma which underwent viscocanalostomy[40]. At 60 months, qualified success (intraocular pressure below 21 mmHg with glaucoma medication) was achieved in 37 (82%) patients and complete success (intraocular pressure below 21 mmHg without medication) in 25 (54%) patients. No sight threatening complications were observed in this series. The authors concluded that viscocanalostomy appears to be a safe and effective intraocular pressure lowering procedure in eyes with primary open angle glaucoma and certain types of secondary open angle glaucoma.

[redacted]

5.2 CANALOPLASTY

The canaloplasty procedure was derived from viscocanalostomy and involves the dilation of 360 degrees of Schlemm's canal with a surgical instrument versus only 60-90 degrees in viscocanalostomy. One such instrument is the iTrack™ Canaloplasty System which received US FDA 510(k) clearance in 2008. The iTrack™ is a flexible microcatheter designed to allow the catheterization and viscodilation of Schlemm's canal to reduce intraocular pressure in adult patients with open angle glaucoma. The procedure does not require placement of an implant or stent and rather than trying to mechanically change or bypass the pathway of aqueous outflow, canaloplasty acts to restore the natural outflow process.

After entry into Schlemm's canal through an *ab externo* approach, a microcatheter is advanced circumferentially using forceps and is used to dilate the canal and the meshwork by injecting microvolumes of viscoelastic during catheterization.

One of canaloplasty's most significant advantages is that it works without a filtering bleb and enables surgeons to reduce or eliminate many of the intra- and postoperative complications associated with trabeculectomy including restrictions on lifestyle, ocular discomfort, over- and under-scarring of the bleb, and infection.

With 10 years of clinical experience behind it, canaloplasty has been evaluated in more than 60 peer-reviewed clinical studies and long term clinical data for canaloplasty have been published. To date, more than 60,000 procedures have been performed worldwide. In the United States, the two procedures (with or without suture) each have their own Medicare Category 1 Reimbursement CPT codes that signify that the procedure is well-established. Like trabeculotomy and viscocanalostomy, canaloplasty is effective at lowering pressure over the long term (not as good as trabeculectomy) but has an improved safety profile over trabeculectomy. [i]

One of the first landmark trials for canaloplasty was a multicenter, prospective trial conducted at 15 clinical sites in the U.S., Great Britain, and Germany.[41] This groundbreaking study included 157 eyes of 157 OAG patients with a baseline pressure of 21mmHg or higher, with many eyes on maximum tolerated medical therapy. Canaloplasty procedures were carried out on 121 eyes while 36 eyes underwent phacocanaloplasty (canaloplasty combined with cataract extraction). The published three-year data from that trial validated the potential benefits of canaloplasty, demonstrating a significant and sustained IOP reduction and reduced need for medications in adult patients with OAG. It also confirmed the excellent short- and long-term safety profile of the procedure. The complications associated with canaloplasty included Descemet membrane detachment, hyphema, cataract formation, IOP spikes, and hypotony.

[redacted]

[redacted]

Notably, sustained hypotony and related complications were not observed. While transient hyphema ≥1.0 mm was the most common complication, occurring in ~10% of eyes, a study by Grieshaber, *et al*. has shown that hyphema can, in fact, be considered to be a sign of successful reconnection with the ocular venous system and, therefore, of a good prognosis.[42]

In 2011, Grieshaber *et al*. also published the results of a prospective study of 32 patients with OAG in which the mean IOP was reduced from 27.3 ± 5.6mmHg preoperatively to 12.8 ± 1.5mmHg at 12 months and 13.1 ± 1.2mmHg at 18 months following surgery.[43]

A more recent study by Brusini of 214 eyes from 185 OAG patients with a maximum of four-year follow-up reported a mean IOP reduction of 42.2%. The percentages of eyes that obtained postoperative IOP≤ 21mmHg, ≤18mmHg, and ≤16mmHg with or without medical therapy after 2 and 3 years were 88.7%, 73.7%, and 46.2% (2 years); 86.2%, 58.6%, and 37.9% (3 years), respectively. The most frequent complications observed included hyphema; Descemet membrane detachment; IOP spikes; and hypotony.[44]

Dr. Norbert Koerber, a renowned glaucoma specialist in Germany, also showed in a study of canaloplasty and viscocanalostomy that both methods were effective at 18 months in reducing IOP from a mean of 24 - 26 mm preoperatively to 14-16 mm postoperatively. Additionally, mean medication use in both groups was reduced from 1.9 – 2.1 medications preoperatively to 0.3 - 0.4 medications postoperatively.[45]

Additionally, a group at the Centre for Ophthalmology, University Hospital Tübingen in Germany published a retrospective case review of all canaloplasty surgeries with a minimum follow-up of 5 years.[46] The surgical procedure followed the technique described by Lewis *et al*. The success of surgical outcome was defined as complete when no additional medication was required or qualified when additional medication was required to achieve the specific intraocular pressure (IOP) definition. Twenty eyes were included in the study. None of the eyes underwent canaloplasty combined with cataract surgery. The mean IOP decreased from 25.7 ± 6.6 mmHg (standard deviation) at baseline to 15.5 ± 3.8 mmHg (n = 19) at 1 year ($P < 0.001$), 15.1 ± 4.4 mmHg (n = 18) at 3 years ($P < 0.001$) and 14.2 ± 3.4 mmHg (n = 18) at 5 years ($P < 0.001$). Mean number of medications decreased from 3.4 ± 0.5 at baseline to 1.5 ± 1.6 at 1 year ($P < 0.001$), 1.6 ± 1.4 at 3 years ($P < 0.001$) and 1.7 ± 1.3 at 5 years ($P < 0.001$). The differences between 1, 3 and 5 years were not significant. The overall complication rate was low. The most common complication was hyphema, which was observed in seven (35%) eyes. Transient hypotony was observed in one (5%) eye, which resolved spontaneously within 1 week after surgery. They reported no cases of endophthalmitis or other sight-threatening complications.

In 2015, a prospective, randomized clinical study of 62 patients with uncontrolled open-angle glaucoma who randomly received trabeculectomy (n = 32) or canaloplasty (n = 30) was published.[47] The primary endpoint was complete (without medication) and qualified success (with or without medication) defined as an intraocular pressure (IOP) of ≤18 mmHg (definition 1) or IOP ≤21 mmHg and ≥20% IOP reduction (definition 2), IOP ≥5 mmHg, no vision loss and no further glaucoma surgery. Secondary endpoints were the absolute IOP reduction, visual acuity, medication, complications and second surgeries. Surgical treatment significantly reduced IOP in both groups ($p < 0.001$). Complete success was achieved in 74.2% and 39.1% (definition 1, $p = 0.01$), and 67.7% and 39.1% (definition 2, $p = 0.04$) after 2 years in the trabeculectomy and canaloplasty group, respectively. Mean absolute IOP reduction was 10.8 ± 6.9 mmHg in the trabeculectomy and 9.3 ± 5.7 mmHg in the canaloplasty group after 2 years ($p = 0.47$). Mean IOP was 11.5 ± 3.4 mmHg in the trabeculectomy and 14.4 ± 4.2 mmHg in the canaloplasty group after 2 years. Following trabeculectomy, complications were more frequent including hypotony (37.5%), choroidal detachment (12.5%) and elevated IOP (25.0%). The study authors concluded that trabeculectomy is associated with a stronger IOP reduction and less need for medication at the cost of a higher rate of complications.

[redacted]

Recently, the iTrack™ microcatheter is being used for *ab interno* canaloplasty to spare the sclera and conjunctiva. Like *ab externo* canaloplasty, *ab interno* canaloplasty addresses the trabecular meshwork, Schlemm canal, and collector channels. It follows the same dilation principles of *ab externo* canaloplasty, where the controlled delivery of viscoelastic during withdrawal of the iTrack microcatheter creates microperforations in the trabecular meshwork and separation of the compressed tissue planes within Schlemm's canal. The procedure pulls any herniated inner wall and juxtacanalicular tissue out of the collector channels. It should be noted that *ab interno* canaloplasty is expected to provide equivalent or better IOP reduction as compared to an *ab externo* approach while avoiding some of the complications observed in the aforementioned studies including inadvertent bleb and suture extrusion through the TM. As mentioned, an *ab interno* approach has the benefit of sparing the conjunctiva, sclera, or limbus for additional surgery (including trabeculectomy or an implantable glaucoma shunt). Therefore, as is the case with laser trabeculoplasty which also spares the conjunctiva, more invasive surgeries for further IOP reduction are available to the patient, if indicated.

6.0 STUDY ENDPOINTS

6.1 EFFECTIVENESS ENDPOINTS

The primary effectiveness endpoint is change in mean diurnal IOP from baseline at 12 months compared between the VISCO360 group and the control group.

Criteria for Failure to Respond
The mean diurnal IOP at 12 months will be imputed for subjects who meet the following criteria:

- IOP persistently below 6mmHg (defined as an intraocular pressure below 6mm that is present on two consecutive follow-up visits after the three-month visit)
- underwent secondary IOP lowering interventions to control IOP (e.g., laser trabeculoplasty, trabeculectomy, shunt or valve placement, iridotomy/iridectomy) prior to the 12-month visit,
- post-operative introduction of an oral carbonic anhydrase inhibitor,[ii]
- no diurnal IOP data collected from the available Month 12 visit,
- underwent other secondary surgical interventions that could affect IOP,
- use of ocular hypotensive medication within 4 weeks of the Month 12 washout visit [iii]

For subjects who meet any of the criteria above, the mean washout diurnal IOP at baseline will be imputed as the mean washout diurnal IOP at 12 months.

[ii] Does not include use in the perioperative period
[iii] If the study subject fails to remember not to use ocular hypotensive medication for the study eye per the required washout period prior to this visit, they can be reinstructed to washout and return for a 12 month washout IOP visit as long as it falls within the specified visit window.

The secondary effectiveness endpoint is the proportion of subjects achieving a ≥ 20% reduction in mean diurnal IOP from baseline at 12 months compared between the VISCO360 group and the control group. A subject is considered a non-responder if they meet any of the following criteria:

- IOP persistently below 6mmHg (defined as an intraocular pressure below 6mm that is present on two consecutive follow-up visits after the three month visit)
- underwent secondary IOP lowering interventions to control IOP (e.g., laser trabeculoplasty, trabeculectomy, shunt or valve placement, iridotomy/iridectomy) prior to the 12-month visit,
- post-operative introduction of an oral carbonic anhydrase inhibitor,[iv]
- no diurnal IOP data collected from the available Month 12 visit,
- underwent other secondary surgical interventions that could affect IOP, and
- use of ocular hypotensive medication within 4 weeks of the Month 12 washout visit [v]

Subjects who meet any of the criteria above will be imputed as failures in the responder analysis at 12 months.

6.2 SAFETY ENDPOINTS

- Best corrected visual acuity (BCVA) changes from baseline;
- Findings from pachymetry, slit lamp, fundus and gonioscopic examinations;
- Rates of ocular adverse events (intraoperative, postoperative);

The counts and percentages of eyes will be summarized for each adverse event. For each reported adverse event, the percentage of eyes (and the corresponding two-sided 95% confidence interval around the difference in rate per binomial distribution) reported with the safety event will be provided.

The primary analysis is the comparison of all adverse events between the investigational device and control groups through 12 months of follow-up.

[redacted]

[iv] Does not include use in the perioperative period
[v] If the study subject fails to remember not to use ocular hypotensive medication for the study eye per the required washout period prior to this visit, they can be reinstructed to washout and return for a 12 month washout IOP visit as long as it falls within the specified visit window.

[redacted]

[redacted]

7.0 STUDY POPULATION

Up to 30 sites will be recruited to participate in the study to assure enrollment in a reasonable timeframe.

7.1 INCLUSION CRITERIA

Only one eye of each subject is eligible and all criteria apply to study eye only unless otherwise indicated.

1. Male or female subjects, 22 years or older.
2. Pseudophakic with Posterior Chamber IOL (PCIOL)
3. Subjects diagnosed with mild to moderate primary open angle glaucoma (POAG). The diagnosis of POAG must include evidence of:
    - Glaucomatous optic nerve damage as evidenced by any of the following optic disc or retinal nerve fiber layer structural abnormalities documented with stereo disc photos:
    - Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles
    - Localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles
    - Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue
    - Disc rim or peripapillary retinal nerve fiber layer hemorrhages

      And/Or

    - Visual field defect consistent with glaucomatous optic nerve damage (substantiated with the Humphrey automated perimeter using the SITA Standard 24-2 testing algorithm). Mean deviation (MD) score must be between -3dB and -12dB

[redacted]

4. Intraocular pressure ≥ 18.0 mmHg and ≤30.0 mmHg and not at the patient's target pressure while on 1-3 topical ocular medications or while not on topical ocular medication due to intolerance of medication or history of poor compliance (Screening Visit). Combination glaucoma medications that consist of two or more glaucoma drugs will have each glaucoma drug component counted as a separate drug.
5. At the Baseline Visit, an unmedicated IOP ≥ 21.0 mmHg and ≤ 36.0 mmHg and ≥ 3.0 mmHg higher than the medicated IOP measured at the Screening Visit
6. Shaffer grade of ≥ III in all four quadrants
7. Subjects able and willing to comply with the protocol, including randomization assignment and all follow-up visits through 24 months.
8. Subject understands and signs the informed consent.

7.2 EXCLUSION CRITERIA

All criteria apply to the study eye unless otherwise noted and both eyes of a single subject need not be eligible):

1. Phakia or aphakia
2. Posterior Capsular Opacification graded as moderate or severe using the sample images provided in Appendix 1. In this case, a laser capsulotomy can be performed and the subject screened again a minimum of two weeks following the capsulotomy.
3. Presence of Anterior Chamber IOL (ACIOL)
4. History of complicated cataract surgery (e.g. vitreous loss, sutured IOL, decentered IOL, etc.)
5. Pre-existing IOL instability
6. Diagnosis of acute angle closure, traumatic, congenital, malignant, uveitic, pseudoexfoliative, pigmentary or neovascular glaucoma
7. Inability to properly visualize angle (due to corneal scar, edema, etc.)
8. Abnormal angle anatomy as determined by gonioscopy (e.g. peripheral anterior synechiae, rubeosis or other angle abnormalities)
9. Conditions associated with elevated episcleral venous pressure such as active thyroid orbitopathy, cavernous sinus fistula, Sturge-Weber syndrome, orbital tumors, orbital congestive disease.
10. The subject would be at significant risk by washout of ocular hypotensive medication including any of the following:
    - Unmedicated IOP after washout period is expected to exceed upper limit of 36.0 mmHg at Baseline visit
    - Presence of afferent pupillary defect in either eye
    - C:D ratio ≥ 0.9 in either eye
    - Requiring oral medications (e.g., acetazolamide) for IOP control in either eye

- Evidence of advanced glaucoma in either eye by 24-2 SITA Standard Humphrey visual field defined as mean deviation (MD) of -12.00 or worse and at least one of the following: (a) On PD plot, greater than or equal to 75% of points depressed below the 5% level and greater than or equal to 50% of points depressed below 1% level; or (b) At least 50% of points (i.e., 2 or more) within central 5 degrees with sensitivity of < 0dB on the dB plot; or (c) Points within the central 5 degrees of fixation with sensitivity < 15dB in both hemifields on the dB plot.
- Visual field defects threatening fixation in either eye defined as any (1 or more) point(s) within the central 5° depressed below the 5th percentile on PD plot unless this/these points are >25 dB on Threshold Values (decibel) plot.

11. Subjects with Snellen best-corrected visual acuity worse than 20/80 in either eye.
12. At Baseline visit, subject has not completed appropriate medication washout, if applicable
13. Inability to complete a reliable 24-2 SITA Standard Humphrey visual field at screening (fixation losses, false positive errors and false negative errors should not be greater than 33%). *A visual field done within 90 days prior to the subject informed consent date and in accordance with the 24-2 SITA Standard requirements can be used for the screening evaluation.*
14. Use of more than 3 ocular hypotensive medications (combination medications count as 2 medications)
15. Use of oral hypotensive medication treatment for glaucoma
16. Previous glaucoma procedure with or without an implantable glaucoma device (including incisional surgery, ALT, iridectomy/iridotomy, etc.). [redacted]
17. Clinically significant sequelae from trauma (e.g., chemical burns, blunt trauma, etc.)
18. History of elevated IOP due to steroid response
19. Use of systemic medications (either current, within 30 calendar days of screening exam, or anticipated) that may cause an increase in IOP, (e.g., systemic steroids including inhaled steroids used on a regular basis)
20. Ocular pathology or medical condition for which, in the investigator's judgment, the following factors would either place the subject at increased risk of complications or contraindicate surgery or interfere with compliance to elements of the study protocol (e.g., ophthalmic examinations, follow-up visits):
    a) inability to reliably complete visual field testing over the course of the study,
    b) uncontrolled systemic disease (e.g. diabetes, hypertension) that could compromise their participation in the study,
    c) disorders that pose a fall risk, as well as compromise ability to take a visual field exam and take glaucoma medications (e.g., Parkinson's disease),

d) inability to discontinue use of blood thinners in accordance with surgeon's standard pre-operative and postoperative instructions,

e) immunodeficiency concerns,

f) other clinically significant ocular pathology other than glaucoma.

21. Proliferative diabetic retinopathy
22. Previous surgery for retinal detachment
23. Central corneal thickness that is less than 450 microns or greater than 620 microns.
24. Clinically significant corneal dystrophy (e.g., bullous keratopathy, guttata, etc.)
25. Previous corneal surgery
26. Wet age-related macular degeneration
27. Clinically significant ocular inflammation or infection ≤ 30 days prior to screening.
28. Participation in any clinical trial ≤ 30 days prior to screening.
29. Women of childbearing potential if they are currently pregnant or intend to become pregnant during the study period; are breast-feeding; or are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study. (A negative serum pregnancy test must be verified for females of child bearing potential). All women are considered to be of childbearing potential unless:

- Postmenopausal for at least 1 year
    - OR
- Surgically sterile

8.0 STUDY PROCEDURES

8.1 INFORMED CONSENT

The informed consent will be presented and explained to each prospective subject by the investigator or a trained clinical professional. The final Informed Consent Document (ICD) must be approved by the Institutional Review Board (IRB) and Sight Sciences, Inc.

Once the subject has been informed of all aspects of the study, the subject will be given a choice to voluntarily confirm his or her participation in the study as documented by completion of the Informed Consent. After signing the Informed Consent, the HIPAA (Health Insurance Portability and Accountability Act) authorization, and other applicable local documentation (e.g., California Bill of Rights), the subject can then proceed with the screening evaluation. The subject has the right to withdraw from the study at any time without consequences, as indicated in the Informed Consent Document.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. Subjects are enrolled upon signing the ICD even if they subsequently fail to meet the eligibility criteria.

The principal investigator(s) must retain the original, signed written Informed Consent Document. A copy of the written Informed Consent Document must be given to the subject.

8.2 SCREENING AND BASELINE EVALUATION

After obtaining an understanding of the purpose of this study, then reviewing and signing the Informed Consent Document, all potential subjects will undergo an initial screening examination in order to determine their eligibility for the study.

If both eyes meet the applicable inclusion and exclusion criteria, the right eye will be selected for the study.

The other eye will be excluded based on the first eye already being included in the study.

[redacted]

8.2.1 RANDOMIZATION

After eligibility has been confirmed and all other procedures in the Screening and Baseline visits have been completed, the subject will be randomized to participate in the Treatment or Control groups using a pseudo-random number generator with subjects enrolled according to a predetermined list based on the subject's prior history of SLT in the study eye (yes or no). Each investigational site will be provided two sets of envelopes with randomization assignments, one for subjects with prior SLT in the study eye and the other for subjects without prior SLT. If the randomization is to be generated via an electronic randomization system (such as the randomization module of an electronic data capture (EDC) system), then the study site will be requested to enter the subject's prior history of SLT into the system in order to obtain the study treatment group assignment from the system. The Treatment group will undergo the VISCO™360 Viscosurgical System procedure. The Control group will receive SLT per the procedure described in this protocol.

Following randomization, the subject should be scheduled to have the study procedure (either VISCO360 or SLT) within 0 to 7 calendar days of the Baseline Visit. In order to prevent possible assignment bias, the randomization envelopes cannot be opened or the randomization system cannot be used all other aspects of the Baseline visit have been completed. **The clinical study staff should make every effort to keep the study subject masked as to the assigned randomization arm until the time of the procedure.**

8.3 TRAINING

Before any site may begin study surgeries, all investigators will participate in a Sight Sciences investigator training session. Each investigator must have read the protocol and Instructions for Use (IFU) for VISCO360 and undergone training under the direct supervision of a Sight Sciences, Inc. representative in the following:

- How to properly unpack the device
- How to properly prime the device
- How to advance and retract the microcatheter
- How to properly dispose of the device

Investigators will also gain familiarity with the VISCO™360 Viscosurgical System through the following:

- Animated video of the procedure demonstrating VISCO360 angle surgery and dilation of Schlemm's canal.
- Live surgical videos of the VISCO360 procedure
- Use of animal or human cadaver eyes in a wet lab. NOTE: This is only required if the Investigator is not familiar with angle surgery. Familiarity with angle surgery is defined as prior live experience with angle surgery and/or confidence with gonioscopic surgical viewing.

Further training will be provided to the study coordinators at each site during the site initiation visits by the study monitors. The first VISCO360 study procedure by each investigator will be done under the direct supervision of a Sight Sciences, Inc. representative.

8.4 MATERIAL AND EQUIPMENT

A listing of general equipment and materials required at the investigational site for the preoperative, operative, and postoperative steps of the investigational study is provided below.

1. [redacted]

The Goldmann tonometer should be calibrated at each investigational site in accordance with the manufacturer's instructions. Each site is also to follow their own standard procedures for equipment maintenance and calibration by outside vendors. Calibration values should be recorded and the documents maintained accordingly.

8.5 VISCO™ 360 VISCOSURGICAL SYSTEM PROCEDURE

The following provides an overview of the perioperative study procedures for the VISCO™360 Viscosurgical System. If possible, each surgical procedure should be videotaped. The approved labels for the OVD's used for anterior chamber maintenance and for the canaloplasty procedure should be reviewed for more information.

[redacted]

Note: Contents are sterile when the package is sealed and undamaged. Do not use if

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.5.3 VISCO360 Postoperative Instructions

Subjects should be advised to keep their heads elevated for 24-48 hours to avoid hyphema formation. They should also be instructed not to engage in extreme lifting or bending.

Patients who are unable to safely discontinue use of blood thinners in accordance with surgeon's standard pre-operative and postoperative instructions should not be enrolled into the study. The subject should discontinue systemic NSAIDs or blood thinners/anti-clotting medication after surgery per the surgeon's usual routine (i.e. POD#1 or when it is medically appropriate in the interest of patient safety).

The following ophthalmic medications should be prescribed for the study eye following VISCO360 surgery:

1. Broad-spectrum antibiotic as per the surgeon's preference for 7 days
2. Pilocarpine 1 drop BID for 4 weeks, if tolerated
3. NSAID (e.g. Ketorolac 0.4%): 1 drop 4 times per day for 4 weeks
4. Prednisolone Acetate 1%: 1 drop 4 times per day for 2 weeks then 2 times per day for 2 weeks before discontinuation (if no evidence of steroid response).

8.6 SLT PROCEDURE

The type of anesthesia will be at the surgeon's discretion.

For patients assigned to the SLT treatment arm, a single application of pilocarpine and apraclonidine (1 %) or brimonidine (0.2 % or 0.15 %) will be instilled into the operative eye prior to the laser treatment. A frequency doubled, q-switched Nd:YAG laser emitting at 532 nm with a pulse duration of 3 ns, a spot size of 400 μm, and pulse energies ranging from 0.6 to 1.6 mJ, coupled to a slit lamp delivery system with a helium-neon laser aiming system will be used in all cases. Any mirrored gonioscopic lens that does not magnify is acceptable for use during the procedure. The laser will be focused on the trabecular meshwork using the HeNe aiming beams and a single laser pulse will be delivered at the 3 o'clock position. The laser energy will be increased or reduced by 0.1-mJ increments until fine 'champagne' bubbles are generated. During laser application, bubble formation will be monitored with each pulse to avoid excessive bubble formation and to avoid no observed response.

Additional details are included in the SLT laser manufacturer's approved instructions for performing SLT.

180° treatments of approximately 50 applications should be applied first inferiorly and then superiorly with the goal of 360° treatment. If necessary, the superior 180° SLT treatment can be performed in a separate session within 1 week of the first SLT session and the reason for deferral should be recorded. The total number of pulses delivered, the number of clock hours treated, and the total amount of energy delivered will be recorded following each treatment.

One drop of apraclonidine (1 %) or brimonidine (0.2 % or 0.15 %) should be applied immediately after the SLT procedure and an NSAID (e.g. Ketorolac 0.4%) 1 drop 4 times per day for 4 days should be prescribed following SLT.

The IOP should be checked and recorded within 1 hour of the laser procedure. An IOP increase ≥ 10 mmHg should be recorded as an AE.

8.7 WASHOUT

Subjects who meet all screening eligibility criteria will be instructed to discontinue their ocular hypotensive medication regimen in the study eye only, and to return for a baseline visit after completing the appropriate washout period. Glaucoma medication discontinuation can be staged so that the pressure increase duration is minimized to the greatest possible extent during the washout period.

If the subject does not currently take any glaucoma medication, the Baseline Exam can be scheduled as soon as two (2) days after completing the Screening Exam.

All subjects on ocular hypotensive medication(s) at Screening and Month 12 will be instructed to undergo a washout prior to the Baseline/Month 12 postoperative visit. If a subject cannot be washed out of their ocular hypotensive medications, the medical monitor will review the subject records and the decision in a masked fashion. If the study subject fails to remember not to use ocular hypotensive medication for the study eye per the required washout period, they can be reinstructed to washout and return for a 12-month washout IOP visit as long as it falls within the specified visit window.

The minimum wash-out periods are specified in **Table 1** below. Note: The maximum washout period is 6 weeks. Therefore, if the surgery/SLT procedure cannot be scheduled within one week of the end of the washout period, the subject should be restarted on glaucoma medication until the Day 0 visit.

TABLE 1: OCULAR HYPOTENSIVE MEDICATION WASHOUT PERIODS

Brand Name/Chemical Name	Minimum washout period
Carbonic Anhydrase Inhibitors	
Diamox® (Acetazolamide) – oral Rx	5 days
Neptazane® (Methazolamide) – oral Rx	5 days
Azopt® (Brinzolamide)	5 days
Trusopt® (Dorzolamide Hydrochloride)	5 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
Zioptan® (Tafluprost)	28 days
Combined Medications	
Combigan® (Brimonidine Tartrate/Timolol Maleate)	28 days
Cosopt® (Dorzolamide Hydrochloride/ Timolol Maleate)	28 days
Simbrinza® (Brinzolamide/Brimonidine Tartrate)	28 days
Other	Contact Sponsor

8.8 MANAGEMENT OF IOP AFTER SURGERY/SLT PROCEDURE

Both groups (treatment and control) should be treated consistently. In general, the primary consideration for management of IOP is the preservation of the retinal nerve fiber layer, optic nerve and visual field.

Ocular hypotensive medication "rescue therapy" will be introduced 1 month postoperatively or later to any subject if his/her IOP increases ≥ 21 mmHg and is ≤ 20% below their preoperative medicated IOP (at two consecutive visits within a two week period).

For subject safety, a change in 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, Medical Monitor and Sponsor at all times is the health and safety of the subjects.

Administration of glaucoma medication in subjects with IOP < 21 mmHg will be considered on a case-by-case basis by the study investigator and the Medical Monitor. In these cases, the Medical Monitor will consult with the physician to understand the rationale for the intervention and it will be documented by the investigator on the follow-up form in the field identified as "Investigator rationale for intervention". For the intervention, the reason for the decision will be noted on the case report form as one or more of the following: "IOP> target IOP", "visual field change", and "optic nerve change". A field for "Other" will be used to document any other reason for the intervention.

Re-introduction of hypotensive medications will be standardized as follows:

- The same medication class(es) as used preoperatively will be re-introduced. Dependent on preoperative IOP medication use, the reintroduction/addition of IOP medications postoperatively should follow the order below:

  1. Prostaglandin Analogues
  2. Alpha Agonists
  3. Beta Blockers
  4. Carbonic Anhydrase Inhibitors (CAIs).

- No more than one ocular hypotensive agent should be added at a single visit or within a 2-week period, without approval of the Medical Monitor. Approval of the Medical Monitor must be obtained prior to or promptly after the subject's visit (e.g. within 3 working days).

In the event of a steroid response (IOP increase), the usual guidelines requiring a reproducible increase in IOP should be followed; however, topical hypotensive medications should be discontinued once the topical steroid has been discontinued.

Use of glaucoma medications in the first month after surgery/SLT will be allowed at the discretion of the study investigator. This short-term use of glaucoma medications in the

immediate postoperative period will not be considered "rescue therapy" and will not be considered in the effectiveness analyses for the study.

If a pressure rise is observed, a paracentesis may be performed as necessary by either the principal investigator or the sub-investigator. If a paracentesis is performed and there is no protocol-defined adverse event, the paracentesis will be documented in the subject's medical record, the applicable visit CRF and the Ocular Procedures log. If, however, the paracentesis is performed in conjunction with an AE, then the AE is recorded as such, and the paracentesis is also recorded on the AE CRF as a treatment for the protocol-defined AE (as well as the other CRFs mentioned above).

Usage of hypotensive medications specifically indicated for prevention of IOP increases following Nd:YAG capsulotomy and administered for up to 72 hours after Nd:YAG capsulotomy, will not be considered rescue therapy.

Medications which have been re-started by the investigator may be discontinued if the investigator's judgment is that the target intraocular pressure has been reached and the continued use of some or all of the therapy may not be required. Discontinuation of medications after re-introduction is recommended to be in the reverse order of re-introduction. The rationale for discontinuation will also be documented on the follow-up form by the investigator and the Medical Monitor will follow up with the investigator as needed to assure consistency within the study parameters. For medication discontinuation, the reason for the decision will be noted on the case report form as "IOP controlled" or "allergy to medication". A field for "Other" will be used to document any other reason for glaucoma medication discontinuation.

A record of all ocular hypotensive 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 Visit, if necessary.

Another potential reason for intervention is hypotony. Intervention should only be considered if the hypotony has caused or is likely to cause sequelae such as a flat chamber. No intervention is indicated when the vision is unchanged from screening, there is no persistent choroidal detachment, the anterior chamber is not flat with lens corneal touch, or the patient is asymptomatic. No intervention should be undertaken for hypotony which is not causing, or threatening to cause, a reduction in vision.

If another glaucoma procedure occurs, the event will result in the subject being followed according to standard of care until the adverse event resolves and the follow-up visits over the two years period under the protocol schedule will be part of the safety analyses. Any extra visits to evaluate the patient due to the secondary procedure will be considered "Unscheduled Visits" if performed outside of the standard visit windows in the protocol and the Unscheduled Visit form will be used to document the visit.

For any surgery or interventions not directly related to the subject's glaucoma that occur during the study, the standard of care for the particular type of intervention will be followed until the subject has recovered. Unless a visit coincides with the standard protocol follow-up visit, the

visits will be handled as "Unscheduled Visits" and the Unscheduled Visit form will be used to document the visit.

8.9 FOLLOW-UP

All subjects will participate in defined follow-up visits throughout two years as follows:

- Screening (Day -45 TO -2)
- Baseline (Day -15 TO 0 after completion of medication washout)
- Surgery/SLT Procedure (Day 0)
  - If necessary, the second 180° SLT treatment can be performed in a separate session within 1 week of the first SLT session and the schedule of visits will not be altered (the Unscheduled Visit CRF will be used for this visit)
- 1 Day Postop (Day 1)
- 1 Week Postop (Day 5-9)
- 1 Month Postop (Day 21-35)
- 3 Months Postop (Day 70-98)
- 6 Months Postop (Day 150 –210)
- 12 Months Postop (Day 330 – 420)
  - At the 12 M Postoperative Visit, only subjects who are ocular hypotensive medication-free will have Diurnal IOP measurements performed. Subjects using ocular hypotensive medications at this visit will undergo medication washout and return for the 12 M Postoperative Washout Visit for Diurnal IOP measurements.
- 12 Month Washout (Day 330 – 420, after completion of medication washout)
- 18 Months Postop (Day 510 – 600)
- 24 Months Postop (Day 690 – 780)

A follow-up case report form shall be completed from source data gathered at the time the subject is examined. Unscheduled visits should also be recorded using the appropriate forms. **Table 2** provides an overview of all activities to be conducted during the clinical study.

All attempts should be made to conduct each follow-up evaluation within the specified time intervals shown in **Table 2**. Evaluations conducted outside the prescribed time period will be considered protocol deviations. Visits conducted outside scheduled timeframes will be considered an additional visit and must be documented using the Unscheduled Visit form.

[redacted]

[redacted]

8.10 WITHDRAWAL CRITERIA

All subjects have the right to withdraw at any point during the treatment without prejudice. The investigator can discontinue any subject at any time if continued participation in the study would result in harm to the subject. All efforts should be made by the investigator to retain the patient in the study. If a subject withdraws prematurely from the study, a genuine effort must be made to determine the reason(s) the subject discontinued the study. The reason must be recorded in the subject's file and on the End of Study Form and faxed to Sight Sciences, Inc. and the CRO (Sierra Clinical Services).

8.11 LOST TO FOLLOW-UP SUBJECTS

Subjects who do not show up for a follow-up must be contacted to attempt to have them come for the follow-up. For those subjects who cannot be reached, at least 3 phone call attempts should be made and documented. If still no response, a registered letter shall be sent to the address on file for the subject in an attempt to make contact. If there is still no response, the subject will be considered lost-to-follow-up unless there is a further communication by the subject.

8.12 DEVICE RETURN

If a Sight Sciences device needs to be returned, the Device Return Form must be completed and returned with the product as instructed by the Device Return Procedure (located in the Regulatory Binder). Reasons for return could include any of the following:

1. Device has exceeded the labeled expiration date.
2. Device was not present or damaged in packaging.
3. Device was damaged or contaminated before or during surgical procedure.
4. Device could not be inserted during surgical procedure.
5. Unused inventory upon completion of the study or site exiting from the study.

For any device to be returned that has been exposed to blood or tissue, a special package will be provided by Sight Sciences, Inc. for return of the device.

8.13 PROTOCOL MODIFICATION AND DEVIATIONS

Protocol modifications may occur during the study. Each will be approved by the sponsor before implementation. Each will undergo Institutional Review Board (IRB) review and approval as necessary.

Any deviations from this protocol intended to protect the life or physical well-being of a subject in an emergency are to be reported to Sight Sciences, Inc. as well as the IRB as soon as possible, and no later than 5 working days after the emergency occurred.

All protocol deviations will be documented using Protocol Deviation form.

9.0 DATA HANDLING AND RECORDKEEPING

9.1 SUBJECT IDENTIFICATION

The subjects will be identified by a seven digit subject number composed of a one-digit study identification number, a three digit center identification number followed by a three digit sequential subject number. The subject identification will be assigned when ICD is obtained. The initials for each subject will also be included on CRFs. In this way, information contained in the study records will be kept as confidential as possible.

9.2 SUBJECT ACCOUNTABILITY

All subjects randomized in this clinical investigation shall be monitored for the duration of the investigation. The clinical investigation shall be considered completed when all subjects that have been enrolled in the investigation, excluding subjects who were withdrawn, have reached the final reporting period.

9.3 CONFIDENTIALITY

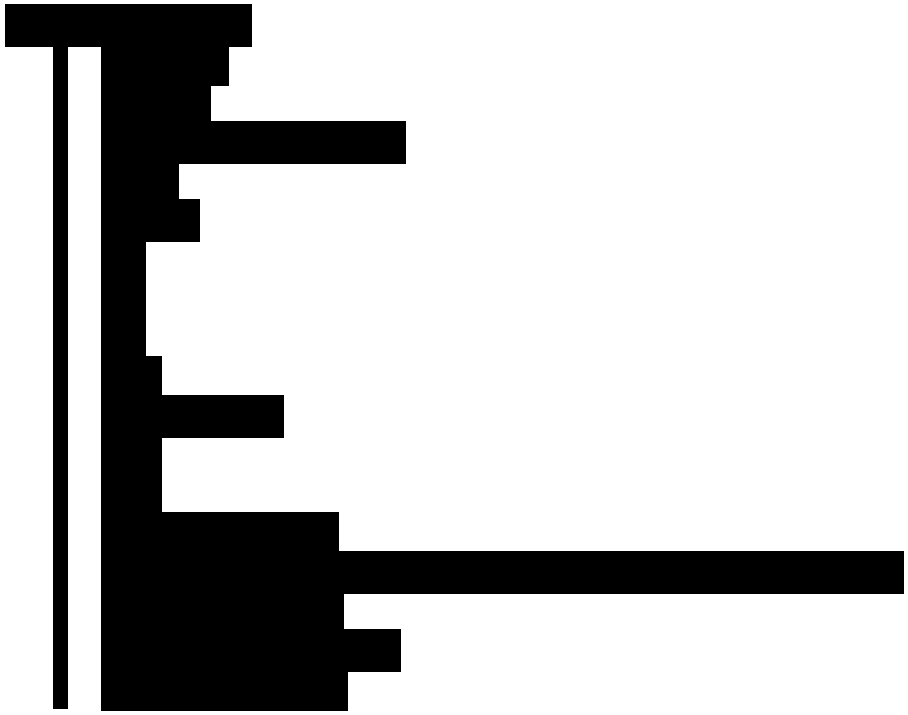
All medical records associated with the clinical investigation will be made available for review by Sight Sciences personnel, its contract research organization (CRO) and governmental/regulatory agencies involved. The results of the study may be published in the future for scientific and marketing purposes, but the identity (name) of each subject will not be revealed. All records will be stored in a secure area at the investigator's facility, the CRO, and at Sight Sciences, Inc.

9.4 SOURCE DATA AND CASE REPORT FORMS

The following forms will be utilized to collect source data during this clinical investigation. Source Data Form Completion Guidelines will be provided at the investigational sites. These guidelines provide added instructions for the completion of all forms. These guidelines will be updated as needed throughout the trial to provide continuing clarification as required.

Source data forms are to be maintained at the site in the subject records. All entries must be made in black or blue ink and changes must be made by strike-through only with date and initials or signature. All source documents must be completed and signed by the authorized study personnel (e.g., study coordinator). No "white-out" is to be used on the source documents.

The source data will be entered into a validated electronic system at each site by trained personnel in accordance with 21CFR Part 11 requirements.



9.5 DEVICE ACCOUNTABILITY

With each shipment of investigational devices, Sight Sciences will include a Packing List that will give the amount shipped and the lot numbers. This packing list must be reconciled by the investigational site with the contents of the shipment and then complete the Inventory Logs for the VISCO™360 Viscosurgical System (these logs are contained within the regulatory binder at the site). All investigational products at the site must be stored in a secured/locked area. Device reconciliation activities will also be conducted periodically in conjunction with site monitoring visits.

The investigator must maintain accurate records of the receipt of all devices shipped by Sight Sciences, including the date and lot numbers received with the use of the device inventory tracking log. The use of devices will also be recorded. An extra label provided with the device may be placed in the patient records.

9.6 RECORD RETENTION

Clinical sites are to retain any and all clinical trial material (documentation, photographs, etc.) for a period of two years from the date the marketing application is approved or two years after the investigation has been discontinued and the FDA notified, or as directed by their institutional document retention requirements, whichever is the longest. After that time, the items must be returned to Sight Sciences for archiving. Unused medical devices are to be returned to the sponsor at the conclusion of the enrollment period.

9.7 DATABASE MANAGEMENT

The database will be designed to be compliant with 21 CFR Part 11 and relevant guidance documents. The electronic database will be developed and maintained by an independent Contract Research Organization.

The database will incorporate time-stamped audit trails, protection of human subjects, restricted access, and data security at the component level. Each database module, including each individual CRF, will be validated by conducting a series of standard tests that demonstrate usability and correctness of the database system. The database will be maintained on an ongoing basis and will be routinely backed up with both onsite and offsite storage.

10.0 ADVERSE EVENTS

Adverse Events are defined below. Adverse events that occur in the study eye during the trial as well as other non-ocular events whether they are considered to be device related or not must be documented in the subject's records. Date of the event, its severity, treatment (if any) and the assessed relationship of the event to the study device will be recorded on the Adverse Event Form. Conditions which exist at the time the subject is enrolled do not need to be recorded on the Adverse Event Form as adverse events unless they increase in severity during the study.

10.1 ANTICIPATED ADVERSE EVENTS

Anticipated adverse events include those that might reasonably be expected to occur in this study because they are associated with glaucoma, SLT laser treatment, and/or the risk analysis for VISCO 360.

[redacted]

[redacted]

10.2 UNANTICIPATED ADVERSE DEVICE EFFECT

Unanticipated adverse device effect (UADE) is defined as any serious adverse effect on the 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 sight-threatening event, whether listed in the protocol or not, is considered to be reportable as a UADE.

10.3 REPORTING ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

All unanticipated adverse device effects (UADE) will be reported to the study sponsor, Sight Sciences, Inc., (877-266-1144) and by e-mail to safety@sightsciences.com and to the reviewing IRB as soon as possible but no later than 10 working days after the investigator first learns of the event. A UADE should be documented as an adverse event using the Adverse Event form and then also documented on the UADE form. All adverse events should be documented by completing the Adverse Event form and, if applicable, a specific IRB AE form.

Identification and collection of adverse event information will be the primary responsibility of the study investigators. The sponsor, the investigator, and the CRO will all follow the Declaration of Helsinki in order to ensure the safety of all subjects.

The sponsor will conduct an evaluation of unanticipated adverse device effects. If the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, parts of the investigation presenting risks will be terminated. Termination will occur not later than 5 working days after the sponsor makes such a determination and not later than 15 working days after the sponsor first received notice of the effect.

10.4 TYPE AND DURATION OF FOLLOW-UP AFTER ADVERSE EVENTS

The investigator is responsible for recommending the type and duration of follow-up for each subject who experiences an adverse event. All events must be followed until complete resolution, resolution with sequelae, or the subject exits from the study. All details must be documented on the Adverse Event Form.

If a subject in either study arm requires an additional glaucoma surgery, the subject shall continue to be seen for the required follow-up visits so that safety and effectiveness can continue to be monitored.

11.0 MONITORING PLAN

Sight Sciences or CRO personnel will monitor the study in a manner consistent with applicable health authority regulations and the clinical research standards adopted by Sight Sciences. Study monitoring will involve the following elements:

- Sight Sciences or CRO personnel meet with investigators and clinical study staff 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.
- Sight Sciences or CRO personnel meet with the investigator(s) and clinical study staff at the time the site begins to enroll in order to ensure that subjects are being properly selected and that study data are being correctly recorded.
- Sight Sciences or CRO personnel visit the clinical site at any time during the study to review and/or collect the Case Report Forms.
- 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.

12.0 STATISTICAL PLAN

The Statistical Analysis Plan for the SightVisco-001 clinical study has been detailed in a separate document. The sample size for the primary effectiveness endpoint and the corresponding statistical hypotheses is based on the following assumptions and criteria.

- The standard deviation of change in mean diurnal IOP from baseline at 12 months is assumed to be 5.0 mmHg. Per Seymenoglu[1], the mean and standard deviation (SD) of the change in IOP from baseline to 12 months was 5.5 mmHg ± 3.8 mmHg for the pseudophakic eyes with SLT, without additional medications, without SLT retreatments, and without any glaucoma-related secondary surgical intervention. Since the study will study the change in the mean diurnal IOP from baseline after washout to 12 months after washout, the SD of the endpoint is expected to be larger than the published SD of 3.8 mmHg. It is assumed an SD of 5 mmHg for the study.
- Significance level is 0.025 (one-sided) and statistical power is 90% at a true mean difference of 2 mmHg.
- Two-sample *t*-test will be used.
- A yearly dropout rate of 10% is considered.
- The randomization ratio for the study is 1:1.

Based on the criteria above, the 12-month sample size for the primary effectiveness endpoint and corresponding statistical hypotheses are **133** VISCO 360 and **133** control subjects at 12 months. With the yearly dropout rate of 10%, approximately **296** subjects (**148** VISCO 360 and **148** controls) should be randomized.

The sample size calculation for the secondary effectiveness endpoint and the corresponding statistical hypotheses described is based on the following assumptions and criteria:

- The 12-month IOP response rates for the control group (p_c) are estimated to be 0.5. Per Seymenoglu, the 12-month IOP response rate was 0.62 for the pseudophakic eyes with SLT, without additional medications, without SLT retreatments, and without any glaucoma-related secondary surgical intervention. Due to the requirement of medication washout in this study, it is expected that the 12-month response rate for the control group of this study is lower than the published 0.62. Therefore, a 12-month response rate of 0.50 is assumed for the control group.
- Significance level is 0.025 (one-sided) and statistical power is 90% at a difference in the responder rate of 0.2. In other words, the power is 90% if the true p_v (the 12-month response rate of the VISCO 360 group) is 0.2 and the true p_c is 0.5.
- Fisher's exact test will be used.
- A yearly dropout rate of 10% is considered.
- The randomization ratio for the study is 1:1.

Based on the criteria above, the 12-month sample size for the secondary effectiveness endpoint and corresponding statistical hypotheses are **134** VISCO 360 and **134** control subjects at 12 months. With the yearly dropout rate of 10%, approximately 298 subjects (149 VISCO360 and 149 controls) should be randomized.

Since the sample size for the secondary effectiveness endpoint is larger than that for the primary effectiveness endpoint, approximately **298 randomized subjects** will be required for this study. If a 40% screening failure is considered, approximately **497** subjects should be enrolled and screened.

13.0 MEDICAL MONITOR

An independent Medical Monitor will be used in the study. The Medical Monitor will not be an investigator in the study. The Medical Monitor will be a certified ophthalmologist with glaucoma specialization. The Medical Monitor will review adverse events and determine if the appropriate action have or are being taken. If a subject cannot be washed out of their ocular hypotensive medications, the medical monitor will review the subject records and the decision in a masked fashion.

14.0 COMPLIANCE WITH PROTOCOL

An investigator shall conduct this investigation in accordance with the signed agreement with the sponsor, the investigational plan, the IDE regulation and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 1: EXAMINATION PROCEDURES, TESTS, EQUIPMENT AND TECHNIQUES

A. MEASUREMENT OF INTRAOCULAR PRESSURE

Each time IOP is measured, the physician or technician is to utilize a Goldmann tonometer; however, the individual operating the tonometer should not view the dial during the measurement and another individual who is masked to the treatment should read the measurement and then record the measurement to minimize observer bias.

Each time IOP is measured, two measurements should be taken and the mean recorded on the case report form unless they differ by more than 2mmHg in which case a third measurement is taken and the median value is recorded. All measurements must be recorded within the source documents.

In order to determine the mean diurnal intraocular pressure (IOP) measurements at baseline and 12 months, values should be taken at 9:00AM ±1.5 hours, 12:00PM ± 1 hour, and 4:00PM ± 2 hours. The three IOP measurements should then be averaged to determine the mean diurnal IOP.

At all scheduled visits except baseline and 12 months, only 1 set of pressure measurements will be needed. Every attempt should be made to have these values taken at the same time interval for each of these other visits.

[redacted]

5. [redacted]

[redacted]

[redacted]

B. VISUAL FIELD EXAMINATION

Visual fields must be automated threshold visual fields, 24-2 Humphrey Stimulus III. The SITA Standard must be used for the visual field conducted at the pre-operative evaluation and all subsequent evaluations. Visual fields must be reliable at screening for eligibility, defined as less than 33% false positives, false negatives, and fixation losses. (These are the acceptance criteria used in the previous OHTS study.) A visual field done within 90 days prior to the subject informed consent date and in accordance with the 24-2 SITA Standard requirements can be used for the screening evaluation. For visual fields that do not meet the reliability standards, the test should be repeated within two weeks.

Visual fields are to be performed with a non-dilated pupil unless, in the opinion of the investigator, the pupil is so miotic that dilation is required (e.g., < 3mm). If dilation was performed at screening, it should be performed at all subsequent visual field examinations. However, dilation should not be performed before the IOP measurement on the appropriate visits.

Visual field interpretation will be documented on the Screening form.

C. PACHYMETRY

Pachymetry should be measured three times during the screening exam utilizing an electronic pachymeter and annually thereafter. These three measurements are to be recorded in the source document and averaged; the mean value should also then be recorded in the appropriate location with the form.

Follow-up measurements conducted at the 12 and 24 month visits should be performed using the same instrument that acquired the screening data if at all possible. These measurements should be performed on the study eye. Three measurements are to be taken and averaged and the mean value recorded on the source documents and transcribed onto the CRF.

D. REFRACTION AND VISUAL ACUITY

Refraction will be performed by the Investigator or staff using standard clinical practice. Refractions will be performed prior to Goldmann tonometry and administration of anesthetic and dilating medication.

Bilateral best-corrected visual acuity using Snellen charts is only performed at screening. The best corrected visual acuity in either eye cannot be worse than 20/80.

A manifest refraction is not required at the one day visit. At all other scheduled follow-up visits, a manifest refraction is required to obtain the best corrected logMAR score.

[redacted]

[redacted]

[redacted]

F. SLIT LAMP EXAMINATION

The clinician will examine the conjunctiva, cornea, anterior chamber, lens and anterior vitreous of the eye with the aid of a slit lamp, which is a table-mounted binocular microscope. Fluorescein dye will be instilled into the ocular cul-de-sac to facilitate this examination. In addition to the following, any evidence of pigment dispersion visible in slit lamp examination should be evaluated and noted.

Iris

Findings of Atrophy/Erosion; Peaking; and Rubeosis should be noted. Each will be evaluated using a scale of None (0), Mild (+1), Moderate (+2) and Severe (+3).

Cornea - Edema

None (0)	Transparent and clear or less than mild
Mild (+1)	Dull glassy appearance
Moderate (+2)	Dull glassy appearance of epithelium with large number of vacuoles
Severe (+3)	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Cornea - Staining/Erosion

None (0)	No fluorescein staining of epithelium, OR less than mild
Mild (+1)	Slight fluorescein staining confined to a small focus
Moderate (+2)	Regionally dense fluorescein staining (1 mm or greater in diameter) with underlying structure moderately visible
Severe (+3)	Marked fluorescein staining or epithelial loss

Anterior Chamber

The following system is recommended for grading of aqueous cells and flare using a slit beam 1.0 mm wide and 1.0 mm long.

Cells

0 = < 1 cell seen
0.5+ = 1-5 cells seen
1+ = 6-15 cells seen
2+ = 16-25 cells seen
3+ = 26-50 cells seen
4+ = > 50 cells seen

Flare

0 = None

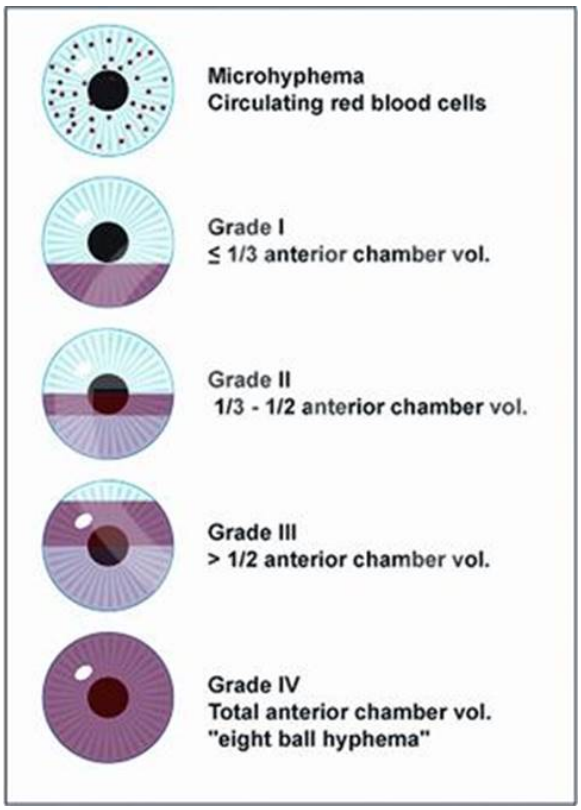
1+ = Faint

2+ = Moderate (iris and lens details clear)

3+ = Marked (iris and lens details hazy)

4+ = Intense (fibrin or plastic aqueous)

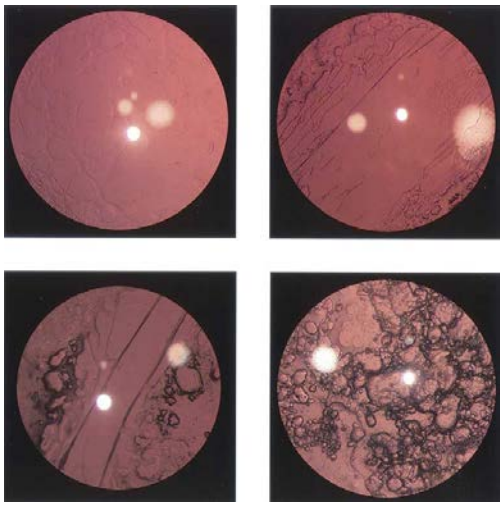
The presence of hypopyon is recorded separately. The presence of "microhyphema" or "layered hyphema" in the anterior chamber should also be recorded. Layered hyphema will be graded using the following scale (If Grade 1, also record size in mm on the CRF).[49]



[49] http://www.aao.org/image/hyphema-grading-system-2

Posterior Capsule Opacification

As a routine part of the slit lamp examination, posterior capsule opacification (PCO) will be evaluated using the following scale:



NONE

Minimal (Top left image)

Mild (Top right image)

Moderate (bottom left image)
Severe (bottom right image)

If a subject with PCO is scheduled for a YAG laser capsulotomy, the subject's best-corrected visual acuity (BCVA) must be measured prior to the YAG procedure and at a subsequent interim visit following the YAG procedure. Additionally, all information related to hypotensive medications prescribed to a subject before or after a YAG procedure must be collected. This information must be captured on the appropriate source document and study case report form.

<u>Other Slit Lamp Findings (complete for each finding)</u>

- Trace
- Mild
- Moderate
- Severe

G. GONIOSCOPY

Gonioscopy will be conducted as part of the screening process to verify that the subject has an open angle and to identify any anterior synechiae as well as determine if there is any pigment dispersion. A Zeiss, Sussman or similar lens should be used and gonioscopy conducted in a dark room with a narrow, short slit beam that does not pass through the pupil and without a fixation light being used. The Shaffer method will be used as follows: grade 4, wide open (35º-45º): grade 3, moderately open (25º-34º); grade 2, moderately narrow (20º); grade 1, very narrow (10º); grade 0, closed (0º). The grade number will be reported for each quadrant of the eye in the appropriate location on the form.

H. OCULAR HYPOTENSIVE MEDICATIONS

Each ocular hypotensive medication will be recorded on the case report form. If subjects are taking combination medications such as Cosopt® this is to be counted as two medications even though this is only in 1 bottle.

I. PREGNANCY TESTING, NURSING AND CONTRACEPTIVES

Women of childbearing potential if they are currently pregnant or intend to become pregnant during the study period; are breast-feeding; or are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study are excluded from participation. A negative serum pregnancy test must be verified for females of child bearing potential. Females of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study. Should this occur, the investigator must immediately contact the sponsor.

J. PATIENT QUESTIONNAIRE (PRO)

A focused questionnaire consisting of 18 questions from the CIGTS "Symptom and Health Problem Chart" (11 Visual Function items and 7 Local Eye items) will be administered.[50,51] The instructions at the beginning of the questionnaire should be followed and the patient responses should be recorded directly on the questionnaire. For each subject, the total score is calculated for Visual Function Symptom Impact (range from 0 to 55) and for Local Eye Symptom Impact (range from 0 to 35). Descriptive statistics such as mean, standard deviation, median, minimum, and maximum will be calculated for each of the two study groups at each visit. No labeling claims will be made based on the PRO's.

[redacted]

APPENDIX 2: SPONSOR'S OBLIGATIONS

GENERAL RESPONSIBILITIES OF SPONSORS

Sponsors are responsible for selecting qualified Investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, and ensuring that each local investigator has obtained IRB review and approval.

SPECIFIC RESPONSIBILITY OF SPONSORS

1. Selecting Investigators - A Sponsor shall select Investigators qualified by training and experience to investigate the device.
2. Obtaining Agreements - A Sponsor shall obtain from each participating Investigator a signed agreement that includes:
   a) The Investigator's curriculum vitae.
   b) Where applicable, a statement of the Investigator's relevant experience, including the dates, location, extent, and type of experience.
   c) A statement of the Investigator's commitment to:
      (1) Conduct the investigation in accordance with the agreement, the investigational plan, and conditions of approval imposed by the reviewing IRB;
      (2) Supervise all testing of the device involving human subjects; and
      (3) Ensure that the requirements for obtaining informed consent are met (21CFR Part 50).

SPONSOR RECORDS

A Sponsor shall maintain the following accurate, complete, and current records relating to an investigation for a period of 3 years after completion of the study:

1. All correspondence with a monitor, an Investigator, an IRB, including required reports.
2. Records of shipment. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and serial number.
3. Signed Investigator agreements.
4. Records concerning adverse device effects (whether anticipated or unanticipated) and complaints.

SPONSOR REPORTS

A Sponsor shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated Adverse Device Effects - A Sponsor who conducts an evaluation of an unanticipated adverse device effect shall report the results of such evaluation to the reviewing IRB and participating Investigator within 10 working days after the Sponsor first receives notice of the effect.
2. Withdrawal of IRB Approval - A Sponsor shall notify the reviewing IRB and participating Investigator of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.
3. Withdrawal of FDA Approval - A Sponsor shall notify the reviewing IRB and participating Investigator of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.
4. Progress Reports - At regular intervals, and at least yearly, a Sponsor shall submit progress reports to all reviewing IRBs.

APPENDIX 3: INVESTIGATOR'S AGREEMENT AND OBLIGATIONS

GENERAL RESPONSIBILITIES OF INVESTIGATORS

An Investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the Investigator's care, and for the control of devices under investigation. An Investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR part 50.

SPECIFIC RESPONSIBILITIES OF INVESTIGATORS

1. Awaiting approval - An Investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB approval.
2. Subject Qualification -The Investigator is responsible for ensuring that all subjects entering the study conform to the patient selection criteria.
3. Compliance - An Investigator shall conduct an investigation in accordance with the signed agreement with the Sponsor, the investigational plan, all applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

INVESTIGATOR RECORDS

A participating Investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation for a period of 3 years after completion of the study:

1. All correspondence with another Investigator, an IRB, the Sponsor, a monitor, or FDA, including required reports.
2. Records of each subject's case history and exposure to the device. Case histories include the study CRF's/worksheets and supporting data including, for example, signed and dated consent forms and medical records. Such records shall include:
    a) Documents evidencing informed consent.
    b) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
3. The protocol, with documents showing the dates and reasons for each deviation from the protocol.
4. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

INVESTIGATOR REPORTS

An Investigator shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated Adverse Device Effects - An Investigator shall submit to the Sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.
2. Withdrawal of IRB Approval - An Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation.
3. Progress - An Investigator shall submit progress reports on the investigation to the Sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
4. Deviations from the Investigational Plan - An Investigator shall document and report to the Sponsor any deviation from the investigational plan.
5. Informed Consent - If an Investigator enrolls a subject without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs.
6. Final Report - An Investigator shall, within 3 months after termination or completion of the investigation or the Investigator's part of the investigation, submit a final report to the Sponsor and the reviewing IRB.
7. Other - An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

APPENDIX 4: DECLARATION OF HELSINKI

I. PREAMBLE

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 be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

II. GENERAL PRINCIPLES

1. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

2. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. Medical progress is based on research that ultimately must include studies involving human subjects.

4. 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 proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

5. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

6. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

7. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

8. Physicians must 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.

9. Medical research should be conducted in a manner that minimizes possible harm to the environment.

10. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

11. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

12. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this 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 patients who serve as research subjects.

13. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

III. RISKS, BURDENS AND BENEFITS

- In medical practice and in medical research, most interventions involve risks and burdens.

  Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

- All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

- Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

  When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

IV. VULNERABLE GROUPS AND INDIVIDUALS

- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

  All vulnerable groups and individuals should receive specifically considered protection.

- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

V. SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

- 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.

- The design and performance of each research study involving human subjects must be clearly described and justified 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, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

  In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

VI. RESEARCH ETHICS COMMITTEES

- The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. 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 amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

VII. PRIVACY AND CONFIDENTIALITY

- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

VIII. INFORMED CONSENT

- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

- In medical research involving human subjects capable of giving informed consent, 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, post-study provisions 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.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

- When seeking informed consent for participation in a research study the physician must 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 must be sought by an appropriately qualified individual who is completely independent of this relationship.

- For a potential research subject who is incapable of giving informed consent, 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 group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

- When a potential research subject who is deemed incapable of giving informed consent 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.

- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must 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 must be obtained as soon as possible from the subject or a legally authorized representative.

- The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

- For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

IX. USE OF PLACEBO

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

  Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

  Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

  and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

  Extreme care must be taken to avoid abuse of this option.

X. POST-TRIAL PROVISIONS

- In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

XI. RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

- Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers 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. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

XII. UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

- In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient 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. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.