Comparison of Silicone and Porous Plate Ahmed Glaucoma Valves

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1. Introduction and Background

Glaucoma with optic nerve damage is usually associated with abnormal elevation of intraocular pressure (IOP) in the eye. Uncontrolled intraocular pressure may result in progressive and painless blindness from optic neuropathy. This damage to the optic nerve is permanent and irreversible. To prevent damage to the optic nerve and subsequent visual field loss, the intraocular pressure in the eye may be lowered using medical and/or surgical intervention.

Glaucoma drainage devices are helpful in the management of intractable glaucoma, which does not respond well to conventional medical and surgical therapies. The Ahmed Glaucoma Valve is a glaucoma drainage device that has a flow-resistive valve mechanism.[1-3] This valve is helpful in minimizing postoperative hypotony and complications associated with hypotony, including flat anterior chamber, choroidal effusions, and suprachoroidal hemorrhage.[4,5]

After Ahmed Glaucoma Valve implantation, patients may require adjunctive anti-glaucoma medications for adequate control of intraocular pressure.[4-6] With smaller glaucoma valve implants, such as the Molteno implant, increasing the device surface area may lead to lower mean intraocular pressure and fewer adjunctive glaucoma medications.[7,8] However, additional surface area does not dramatically improve the results with larger implants, such as the Ahmed Valve and the Baerveldt implant.[9-12] In contrast with trabeculectomy, use of adjunctive mitomycin C does not appear to improve the results with the Ahmed Glaucoma Valve.[13]

In experimental studies, different glaucoma drainage implant plate materials may influence capsule formation and influence the results of glaucoma drainage implants.[14,15] In clinical comparisons, different plate materials have been associated with significant difference of mean postoperative intraocular pressure in some[16-18] but not in all studies.[19,20] In a randomized prospective trial, transient elevation of intraocular pressure during the early postoperative period,

known as a "hypertensive phase," was less frequent after silicone plate compared with polypropylene plate Ahmed Glaucoma Valve implantation.[16] In addition to implant plate size and material, other variables influencing success of glaucoma drainage implant surgery have been identified, including race, treatment with silicone oil endotamponade, and neovascular glaucoma.[21]

A silicone plate Ahmed Glaucoma Valve has demonstrated efficacy and safety in clinical studies.[16-20] An Ahmed Glaucoma Valve plate constructed with porous material, which is Food and Drug Administration (FDA) approved, but has not been studied in clinical trials, may offer advantages in reducing encapsulation of the implant, thereby potentially improving postoperative intraocular pressure control.

2. Device Description

Glaucoma drainage implants used in this study are the Ahmed Glaucoma Valve (New World Medical, Inc., Rancho Cucamonga, CA) Model FP7 (silicone plate, 184 mm^2 surface area) and Model M4 (porous polyethylene plate, 191 mm^2 surface area). Both the Model FP7 and Model M4 are Food and Drug Administration-approved for implantation in humans with intractable glaucoma. Both of these valves will be supplied free of charge by New World Medical Inc for use in this study. Each participating site will be responsible for obtaining FP7 and M4 valves from New World Medical. The valves will not be shipped to UVA and then distributed to participating sites.

The Model M4 plate is approximately the same size as the Model FP7 plate (191 mm^2 and 184 mm^2 surface area, respectively). However, the theoretical surface area of the M4 is much higher because of the porous nature of the material. The porous polyethylene material is formed by a proprietary process (Porex Corporation, Fairburn, GA). The porous plate material is high density polyethylene with a long history of use in surgical implants (MEDPOR Biomaterial implants). Average pore sizes are greater than 100 micro-meters and pore

volume is in the 50 percent range, with an interconnecting open pore structure that allows for tissue ingrowth.

3. Study Objective

To evaluate and compare the clinical outcomes after implantation of the porous plate (polyethylene) Ahmed Glaucoma Valve with the silicone plate Ahmed Glaucoma Valve in subjects with intractable glaucoma.

4. Study Hypothesis

Eyes undergoing implantation with the porous plate Ahmed Glaucoma Valve are less likely to develop an elevation of intraocular pressure during the post-operative period and subsequently will have lower intraocular pressure and possibly require fewer glaucoma medications as compared with the silicone plate Ahmed Glaucoma Valve.

5. Study Endpoints

All study endpoints refer to the selected study eye only and are measured from Baseline to 12 months post-operative in the porous plate Ahmed Glaucoma Valve group as compared to the silicone plate Ahmed Glaucoma Valve group.

5.1 Primary Endpoint

The primary endpoint is the mean intraocular pressure in the porous plate group as compared to the silicone plate group at 12 months.

5.2 Secondary Endpoints

(a) The mean number of anti-glaucoma medications in the porous plate group as compared to the silicone plate group at 12 months.

(b) Surgical success in the porous plate group as compared to the silicone plate group at 12 months. Surgical success is defined as:

Unqualified surgical success: 5 mmHg < intraocular pressure < 22 mmHg with no loss of light perception and no additional glaucoma procedures or glaucoma medications.

Qualified surgical success: 5 mmHg < intraocular pressure < 22 mmHg with no loss of light perception and no additional glaucoma procedures, but with the adjunctive use of glaucoma medications.

6. Study Synopsis

Title:	Comparison of Silicone and Porous Plate Ahmed Glaucoma Valves
Study Period:	12 months, 9 visits: Screening/Baseline; Day of Surgery; Post-Operative Days 1 and 7; and Post-Operative Months 1, 3, 6, 9, and 12. Unscheduled visits will be performed and recorded as required for the optimal treatment and follow up of the subject.
Study design:	A prospective, two-arm, unmasked, randomized, controlled study.
Objectives:	A prospective, randomized trial to evaluate and compare the clinical outcomes after implantation of the porous plate (polyethylene) with the silicone plate Ahmed Glaucoma Valve in subjects with intractable glaucoma.
Control Arm:	Subjects undergoing surgery with the silicone plate Ahmed Glaucoma Valve (Model FP7)
Treatment Arm:	Subjects undergoing surgery with the porous plate Ahmed Glaucoma Valve (Model M4)
Subject Population:	Patients with intractable glaucoma who are candidates for valve surgery.
Sample Size:	Total of 88 subjects with a planned 40 subjects in each arm. Each site can enroll a maximum of 40 subjects.
Follow-up duration:	12 months.

7. Study Population

This is a prospective, two-arm, unmasked, randomized, controlled study of 80 enrolled subjects with intractable glaucoma that have not responded to conventional medical and surgical therapy. The study will accrue up to 88 subjects to allow for a dropout rate of 10 %.

7.1 Inclusion Criteria

- Male or female of any race ≥18 years ≤ 80 years of age.
- Diagnosis of intractable glaucoma in the study eye, with the exception of silicone oil endotamponade induced glaucoma, which has not responded to conventional medical and surgical therapy.
- Elevated intraocular pressure > 21 mmHg in the study eye. Two consecutive measurements using Goldmann Applanation Tonometry will be obtained and the mean of those two measurements will be considered the subject's baseline intraocular pressure.
- Subject is a candidate for surgery in the study eye with a glaucoma drainage device.
- Subject is willing and able to sign the informed consent.

7.2 Exclusion Criteria

- Diagnosis of silicone oil endotamponade induced glaucoma in the study eye.
- History of prior drainage implant surgery in the study eye.
- History of cyclophotocoagulation of the study eye.
- Pregnancy.
- Prisoner.

Eligible subjects may have significant conjunctival scarring, precluding trabeculectomy in the study eye. Presence of diabetes mellitus, prior ocular surgery (with the exception of prior drainage implant surgery) or laser treatment for glaucoma, and use of glaucoma medications in the study eye will be noted, but are not exclusion criteria for determining eligibility.

8. Study Design

8.1 Screening Visit / Baseline Evaluation (Days -60 to -1)

After obtaining informed consent in the patient's, all potential subjects will undergo a baseline examination to determine study eligibility. Standard-of-care evaluations for glaucoma patients that are documented by the investigator may be utilized as the baseline evaluation to determine subject eligibility, provided the evaluations occur within 60 days prior to the planned surgical intervention, even if these evaluations occur prior to the subject consenting to participate in the study. This avoids the potentially unnecessary repetition of screening evaluations that are a part of the standard-of-care for glaucoma patients.

The following examinations, tests, and procedures are required as part of the baseline evaluation to determine subject eligibility and must be conducted within 60 days of the planned surgical intervention:

- Signing of the informed consent
- Review of Inclusion / Exclusion Criteria
- Demographic Information (Date of Birth, Sex, Self-Identified Ethnicity)
- Type of Glaucoma (Diagnosis)
- Review of Medical and Ocular Surgical History
- Review of Concomitant Systemic Medications
- Review of Concomitant Glaucoma Medications
- Review of History of Previous Glaucoma Treatments (laser and surgery)
- Review of Other Concomitant Ocular Medications
- Manifest Refraction and Snellen Visual Acuity
- Intraocular Pressure
    - Intraocular Pressure will be measured utilizing Goldmann applanation tonometry. Two consecutive measurements will be obtained and the mean of those two measurements will be considered the subject's baseline intraocular pressure. The intraocular pressure should be performed at the same time of day at all visits, when possible.
- Slit Lamp Examination
- Gonioscopy

- Funduscopic Examination
- 30-2 or 24-2 SITA Standard Humphrey Visual Field (if available, and may be used if obtained within 12 months of the planned surgical intervention)
- Determination of the study eye and subject eligibility (if both eyes qualify, the study eye will be the eye with the highest baseline intraocular pressure, then worst baseline visual acuity, then the right eye; unless in the investigator's best judgment the other eye should be selected)
- Urine or Serum Pregnancy Test for women of child-bearing potential (to be conducted as part of the site's standard pre-operative testing). The test must be negative to be eligible to participate.

All ophthalmic tests and examinations are for the selected study eye only.
If the subject satisfies all inclusion and exclusion criteria, the subject will be enrolled into the study.

8.2 Surgical Procedure (Day 0)

The surgical procedure must be performed within 60 days of the completion of the screening evaluation. The subject will be randomized to undergo surgical intervention with either the Model FP7, Silicone Plate Ahmed Glaucoma Valve (Group A) or the Model M4, Porous Plate Ahmed Glaucoma Valve (Group B), using the sealed envelope method of randomization. Randomization will take place on the day of surgery.

The following steps are considered guidelines for implantation of both the Model FP7 and Model M4. However, the use of any specific surgical technique or maneuver is at the sole discretion of the surgeon.

1. The implant should be examined and primed prior to implantation. Priming is accomplished by injecting 1cc balanced salt solution or sterile water through the drainage tube and valve, using a blunt 26 gauge cannula.

2. A fornix-based incision is made through the conjunctiva and Tenon's capsule. A pocket is formed at the superior quadrant between the medial or lateral rectus muscles by blunt dissection of Tenon's capsule from the episclera.
3. The valve body is inserted into the pocket between the rectus muscles and sutured to the episclera. The leading edge of the device should be at least 8-10mm from the limbus.
4. The drainage tube is trimmed to permit 2-3mm insertion of the tube into the anterior chamber. The tube should be bevel out to an anterior angle of 30° to facilitate insertion.
5. A paracentesis is performed and the anterior chamber is entered at the limbus with a sharp 23 gauge needle, parallel to the iris. Caution: Care must be taken to ensure that the drainage tube does not contact the iris or corneal endothelium after insertion.
6. The drainage tube is inserted into the anterior chamber approximately 2-3mm, through the needle track and parallel to the iris. The leading edge of the device should be 8-10mm from the limbus.
7. The exposed drainage tube is covered with a small piece of preserved, donor sclera or pericardium, which is sutured into place and the conjunctiva is closed. Note: As an alternative, a 2/3 thickness limbal-based scleral flap may be made. The tube is inserted into the anterior chamber through a 23 gauge needle puncture made under the flap. The flap is sutured closed.

8.3 Post-Operative Follow-Up Visits (1 Day; 7 Day; 1, 3, 6, 9, 12 months)

Follow-up visits will be conducted at the following post-operative time points:

- 1 Day Post-Operative (1 Day + 1 day)
- 7 Day Post-Operative (7 Days +/- 4 days)
- 1 Month Post-Operative (30 Days +/- 7 days)
- 3 Months Post-Operative (90 Days +/- 14 days)

- 6 Months Post-Operative (180 Days +/- 14 days)
- 9 Months Post-Operative (270 Days +/- 14 days)
- 12 Months Post-Operative (360 Days +/- 28 days)

The following examinations, tests, and procedures are required at each post-operative follow-up visit:

- Review of Adverse Events and Assessment of Device Complications
- Review of Concomitant Systemic Medications
- Review of Concomitant Glaucoma Medications
- Review of Other Concomitant Ocular Medications
- Snellen Visual Acuity and Manifest Refraction (per clarification in Administrative Letter #2 dated Oct 3, 2013, Manifest Refraction is optional).
- Intraocular Pressure
  - Intraocular Pressure will be measured utilizing Goldmann applanation tonometry. Two consecutive measurements will be obtained. The intraocular pressure should be performed at the same time of day at all visits, when possible.
- Slit Lamp Examination
- Gonioscopy (at Months 3, 6, 9, and 12 only)
- Funduscopic Examination
- Ultrasound biomicroscopy or Anterior Segment Optical Coherence Tomography to measure the capsule thickness around the plates (Months 6 and 12 only) (optional)

Post-Operative Follow-Up Visits (1 Day; 7 Day; 1, 3, 6, 9, 12 months)
All ophthalmic tests and examinations are for the selected study eye only.

8.4 Unscheduled Visits

Additional (unscheduled) visits will be performed and recorded as required for the optimal treatment and follow-up of the subject. The tests, exams, and

procedures required at the unscheduled visit are dependent upon the reason for the unscheduled visit and will be performed at the investigator's discretion. The following tests, exams, and procedures may be conducted at the unscheduled visit:

- Review of Adverse Events and Assessment of Device Complications
- Review of Concomitant Systemic Medications
- Review of Concomitant Glaucoma Medications
- Review of Other Concomitant Ocular Medications
- Manifest Refraction and Snellen Visual Acuity
- Intraocular Pressure
    - Intraocular Pressure will be measured utilizing Goldmann applanation tonometry. Two consecutive measurements will be obtained. The intraocular pressure should be performed at the same time of day at all visits, when possible.
- Slit Lamp Examination
- Gonioscopy
- Funduscopic Examination
- Ultrasound biomicroscopy or Anterior Segment Optical Coherence Tomography to measure the capsule thickness around the plates (Months 6 and 12 only)

8.5 Early Withdrawal

All subjects have the right to withdraw from the study at any point. The site investigator or the Medical Monitor may discontinue a subject from the study for any of the following reasons:

a. Noncompliance with the study requirements
b. At the discretion of the Investigator or Medical Monitor, due to subject safety concerns.

If a subject withdraws prematurely from the study, a genuine effort must be made to determine the reason(s) for the subject's early discontinuation and the subject should complete an Early Withdrawal visit, which includes the

same tests, exams, and procedures required at the Month 12 Post-Operative Visit.

8.6 Schedule of Visit Tests and Procedures

	SCR[2]	Day 0	POD 1	POD 7	Mo 1	Mo 3	Mo 6	Mo 9	Mo 12/ Early Term	Un-sched Visit
Informed Consent	X									
Inclusion/ Exclusion Criteria Review	X									
Demographic Information	X									
Glaucoma Diagnosis	X									
Review of Medical & Ocular Surgical History	X									
Review of Concomitant Systemic Medications	X									
Review of Concomitant Glaucoma Medications	X									
Review of History of Previous Glaucoma Surgeries	X									
Review of Other Concomitant Ocular Medications	X									
Manifest Refraction & Snellen Visual Acuity	X		X	X	X	X	X	X	X	X[3]
Intraocular Pressure	X		X	X	X	X	X	X	X	X[3]
Slit Lamp Examination	X		X	X	X	X	X	X	X	X[3]
Gonioscopy	X					X	X	X	X	X[3]
Funduscopic Examination	X		X	X	X	X	X	X	X	X[3]
Visual Field Test	X									
Study Eye Determination	X									
Pre-operative tests (labwork, EKG, physical exam) [1]	X									
Randomization		X								
Surgical Intervention		X								
Concomitant Medication Review			X	X	X	X	X	X	X	X[3]
Adverse Event Review			X	X	X	X	X	X	X	X[3]
Ultrasound Biomicroscopy or Anterior Segment OCT[3]							X	X	X	X[3]

1. A serum or urine pregnancy test is required for women of child-bearing potential only, prior to randomization.
2. All Screening Exams must be completed within 60 days of the planned Surgical Intervention, except the visual field test which must be completed within 12 months of the planned Surgical Intervention.
3. Optional.

9. Concomitant Medications and Procedures

9.1 Prohibited Concomitant Medications

There are no prohibited concomitant ocular or non-ocular medications during participation in this study.

9.2 Glaucoma Medication Management

Use of topical or systemic glaucoma medications will be documented at baseline and throughout the post-operative follow-up period for the study eye. Glaucoma medications for the study eye should be suspended only on the day of surgery and reinstituted, if indicated, with necessary adjustments after surgery to manage any elevated intraocular pressure in the study eye. The decision to re-institute glaucoma medications in the study eye will be made at the discretion of the investigator.

9.3 Post-operative Medications

Selection, dosage, and frequency of the study eye post-operative topical antibiotic agent and post-operative anti-inflammatory agent will be made at the discretion of the investigator. All prescribed post-operative ocular medications must be recorded in the study records.

9.4 Device Explant, Repositioning, or Replacement

The device may be revised, repositioned, removed, or replaced by the same kind of device or another marked drainage device if the original device was damaged or determined to be not functioning. If surgical intervention for repositioning or replacement is required, the subject will be required at a minimum to complete all of the protocol required post-operative visits. If sequalae persist, the subject should be followed until all sequalae are considered to be stabilized or resolved.

10. Safety

At each visit, the ocular health of the subject will be assessed. The cornea, anterior chamber, trabecular meshwork, device implant location (if available), and fundus will be examined. Any ocular unanticipated adverse events occurring during the study whether they are considered to be device related or not, must be documented on the Adverse Event Case Report Form. Date and time of the event, event severity, treatment (if any), and the assessed relationship of the event to the study devices will be recorded on the Adverse Event Case Report Form. Conditions that exist at the time the subject is enrolled in the study do not need to be recorded on the Adverse Event Form as adverse events, unless they increase in severity during the study and constitute an unanticipated adverse event..

The collection and recording of unanticipated adverse events will begin at the start of the surgical intervention and will end at the subject's Month 12 or Early Termination Visit. Unanticpated adverse events must be followed until the adverse event has recovered or recovered with ongoing sequelae that will likely not change in the view of the investigator. This period *may* extend beyond study termination.

A brief overview of the differences between anticipated, unanticipated and serious adverse events is provided.

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 surgical procedures. Anticipated adverse events for both the porous plate and silicone plate glaucoma valves include:

* Wound Leak
* Shallow Anterior Chamber

* Flat Anterior Chamber
* Choroidal effusion
* Exposure of Tube, Patch Graft, Plate
* Severe Inflammation
* Tube and/or Flow Obstruction
* Corneal Edema
* Motility Disturbance (i.e. Diplopia)
* Suprachoroidal hemorrhage
* Hypotony (≤ 5 mmHg)
* Elevated intraocular pressure
* Retinal Detachment

10.2 Unanticipated Adverse Events

Unanticipated adverse events include any serious adverse effects on health or safety or any life-threatening problem or death caused by or likely directly related to the Ahmed Glaucoma Valve (M4 or FP7) or the placement of the Ahmed Glaucoma Valve (M4 or FP7) within the eye that are not typically associated with glaucoma surgical procedures.

10.3 Serious Adverse Events

Serious adverse events include those events that require (≥ 24 hours) or prolong hospitalization, require surgical intervention, are sight or life-threatening or fatal, or result in significant disability or incapacity.

10.4 Assessment of Adverse Event Severity

The investigator will make an assessment of event severity for each unanticipated adverse event and serious adverse event reported during the study according to the following definitions:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with the subject's normal everyday activities.

Severe: An event that prevents the subject's normal everyday activities.

10.5 Reporting Adverse Events

Identification and collection of anticipated and unanticipated adverse event information is the responsibility of the study investigator. All unanticipated adverse events should be documented by completing the Adverse Event Case Report Form. and submitted to the study coordinating site per study Manual of Procedures. All adverse events **(whether anticipated or unanticipated)** should be reported to the Institutional Review Board according to site guidelines.

The identification and collection of serious adverse events is the responsibility of the study investigator. All serious adverse events should be documented by completion of the Serious Adverse Event Case Report Form. All Serious Adverse events should be reported to the Medical Monitor within 24 hours of the site's notification of the event and to the Institutional Review Board according to site guidelines.

10.6 Follow-up of Adverse Events

The investigator is responsible for recommending the type and duration of follow-up for each subject who experiences an adverse event. All unanticipated events must be followed until study completion or adverse event resolution or stabilization of adverse event sequelae if the unanticipated adverse event(s) persists post study completion. All follow-up must be documented and submitted to the study coordinating site via the Adverse Event Case Report Form within the appropriate time frames per the study Manual of Operations.

10.7 Aggregate Review of Adverse Events

The Medical Monitor will be responsible for the continuous review of unanticipated adverse events.

11. Statistical Considerations

This prospective, two-arm, unmasked, randomized, controlled trial will evaluate and compare the clinical outcomes after implantation of the porous plate (polyethylene) Ahmed Glaucoma Valve (M4) with the silicone plate Ahmed Glaucoma Valve (FP7) in patients with intractable glaucoma. Subjects will be randomized in a 1:1 ratio to one of two surgical intervention arms - surgical intervention with the Model FP7, Silicone Plate Ahmed Glaucoma Valve (Group A) or the Model M4, Porous Plate Ahmed Glaucoma Valve (Group B). The computer-generated randomization scheme (using varying block sizes of 2 to 4) will be completed by a staff member of the University of Virginia, Department of Ophthalmology, whose sole role in this study is to generate the randomization scheme. The subject surgical intervention arm assignment will be placed in a sealed envelope, securely delivered to the sites, and will be accessed by the site study staff in the site Surgical Admission Suite immediately prior to local anesthesia injection for the surgical procedure. Post-randomization, the assigned surgical intervention arm will be unmasked to the subject.

11.1 Sample Size Considerations

With a sample size of 40 in each group, the power of the study will be 0.8 (80%) to detect a 1.5 mmHg difference in intraocular pressure with a standard deviation of 3 mmHg. Investigators will screen and treat patients .until the study is fully enrolled or the study is terminated. All subjects undergoing surgical intervention will be entered in the statistical analysis. Based on prior studies, failure to complete the 12 month post-operative period is not likely to exceed 10% of randomized subjects.

11.2 Assessment of the Primary Endpoint

The primary efficacy endpoint is the mean intraocular pressure in the porous plate group as compared to the silicone plate group at 12 months The analysis will compare the changes of intraocular pressure after the surgical intervention in the porous plate group as compared to the silicone plate group. Baselines will be compared to check for statistically significant differences and, if needed, a change from baseline analysis will be performed. The statistical significance of the differences in intraocular pressure will be determined using two-tailed paired t-tests.

11.3 Assessment of the Secondary Endpoints

Thesecondary endpoint is the mean number of anti-glaucoma medications and surgical success in the porous plate group as compared to the silicone plate group at 12 months. The baseline number of medications will be compared to check for statistically significant differences and, if needed, a change from baseline analysis will be performed. The statistical significance of the differences in the number of medications will be determined using two-tailed paired t-tests. The mean number of medications at individual time points will be compared in the two groups. Kaplan-Meier survival analysis will be performed for statistical analysis of success rates, with comparisons of groups using the log rank test. Complications will be compared using comparison of proportions (z) test.

11.4 Accrual

Maximum study accrual is estimated to be 88 subjects to accrue the targeted 80 subjects required to meet the study objectives. Maximum accrual allows for a 5% ineligibility rate and a 5% rate of coming off study before the planned surgical intervention. Once target accrual is reached, the study allows those within the screening process to be enrolled. As this allowance is not to exceed 4 patients, up to 84 patients may be treated with Ahmed Glaucoma Valves. Based upon accrual rates to prior drainage

implant studies, accrual is estimated at 15 per month; thus, accrual to the study should be completed in less than 6 months.

11.5 Plans for Interim Analysis

There will be no formal interim analysis. However, for purposes of safety and surgical failures only, unanticipated adverse events will be reviewed periodically by the Medical Monitor to detect a statistically significant increase of vision-threatening complications (e.g., suprachoroidal hemorrhage, endophthalmitis, and surgical failures. If vision-threatening complications and surgical failures exceed a threshold of 30% during the study, consideration will be given by the Medical Monitor to terminate the study early.

11.6 Plans for Final Analysis

Subjects will be monitored until they complete the study period. Primary analysis will include all subjects undergoing the study surgical intervention. All subjects who receive any study intervention will be monitored for adverse events. Adverse event information will be tabulated by type and severity of adverse events. If the subject is determined to be a treatment failure (e.g., increased intraocular pressure, hypotony, loss of light perception vision, or additional glaucoma surgery), this will be documented in the study database.

11.7 Rules for Termination of Study

The Medical Monitor will conduct periodic reviews of unanticipated adverse events and will terminate the study as necessary.

12. Recruitment

To allow the coordinating site to monitor accrual, all study sites must email the coordinating site prior to the randomization of each subject. No other

study documentation needs to be sent to the coordinating site at this time point.

13. Good Clinical Practice (GCP) Compliance

This study will be conducted in accordance with Good Clinical Practice (GCP) using the guidance documents and practices offered by the International Conference on Harmonization (ICH) and United States Food and Drug Administration (FDA), and in accordance with site local regulations.

14. Retention of Records

The site investigator is responsible for maintaining intact study records for a period of at least 6 years following the completion of the study. Study records may be retained for a longer period if specified by local policies.

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