Guidance for Industry and for FDA Reviewers/Staff

Aqueous Shunts - 510(k) Submissions

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Intraocular and Corneal Implants Branch
Division of Ophthalmic Devices
Office of Device Evaluation

Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to Ms. Claudine Krawczyk, HFZ-460, 9200 Corporate Blvd., Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Ms. Claudine Krawczyk at (301) 594-2053 or by electronic mail at cdh@cdrh.fda.gov.

Additional Copies:

World Wide Web/CDRH home page: http://www.fda.gov/cdrh/ode/aqshunt.pdf or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 2236 when prompted for the document shelf number.

I. Introduction

A. Scope

This guidance document serves as a special control for the regulation of aqueous shunts through the submission of premarket notifications [510(k)s]. This guidance does not pertain to devices intended for use in patients with open-angle glaucoma or other conditions not included in the "Indication(s) for Use" described below.

B. Device Description

Name:	Aqueous Shunt (Eye Valve Implant)
Class:	886.3920 (III, proposed reclassification to II)
Panel:	Ophthalmic (OP)
Procode:	KYF

An aqueous shunt is defined as an implantable device intended to reduce intraocular pressure in the anterior chamber of the eye.

C. Intended Use and Indication(s) for Use

The aqueous shunt is intended to reduce intraocular pressure in neovascular glaucoma or glaucoma where medical and conventional surgical treatments have failed.

II. Pre-clinical Data

The following recommendations apply to the aqueous shunt in its final form, after sterilization, as it is intended for implantation. Where appropriate (e.g., with certain biocompatibility tests), the material used in the tests may be a sample of the material fabricated and processed in a manner equivalent to that used for the aqueous shunts. The manufacturer should establish and document equivalency in material and in test sensitivity, where appropriate, for the test sample and the sterile finished aqueous shunt.

A. Physical stability: The functional and dimensional properties of the aqueous shunt should be demonstrated to be stable with all test parameters within tolerance after immersion in distilled water for 14 days at a temperature of 37°C +/- 2°C.

B. Pressure/flow characteristics: The resistance and pressure/flow characteristics of the device under physiological conditions should be substantially equivalent to that of a predicate device. The opening and closing pressures of valved devices in an aqueous environment should be within tolerances of the designed target. The shunt should be free of leaks during testing. Appendix A describes recommended test methods for determining the theoretical flow characteristics of these devices.

C. Structural integrity: The junctions of any components of the aqueous shunt should be able to withstand a force of 0.5 N without breaking or resulting in the loss of the leak-free junction.

D. Biocompatibility recommendations: The aqueous shunt should be evaluated for biological safety. The general recommendations specified in FDA's Office of Device Evaluation (ODE) Guidance Memorandum #G95-1 should apply, together with the following particular recommendations. The following in vivo and in vitro tests should be used to assess the biocompatibility of the aqueous shunt material and to quantify and evaluate the toxicity of biologically active chemical entities that may diffuse out of the finished device material.

- Intramuscular implantation (including macroscopic and microscopic evaluation);
- Animal ocular implantation of device in designed configuration (minimum 6 animals with data to six months). Appendix B contains a test procedure that may be used to perform the animal ocular implantation study;
- Cytotoxicity test
  - Saline and cotton seed oil extracts
  - Cell growth inhibition test (9 point)
  - Aqueous extract (MEM elution)
- Sensitization test
  - Guinea pig maximization
- Intracutaneous test
- Mutagenicity

E. Chemical testing: For silicones, the composition of the basic formulation should have any volatile elements (molecular weight less than 1,000) reduced to not greater than 1.0 wt% by gravimetric method to minimize the potentially leachable compounds.

For PMMA and other polymers, the level of residual monomers should be no greater than 1.0 wt%, determined for the finished aqueous shunt using an exhaustive extraction method with an appropriate solvent to swell the device material.

F. Aqueous aging test: Aqueous shunt materials should be evaluated for monomer content, molecular weight, and identification and quantification of degradation products following aqueous aging. ANSI Z80.7 - 1994 Annex A describes a method that may be used to perform this test. The shunt should be stable in all test parameters within tolerances for equivalent to a one-year period.

G. Dimensional and surface quality: All of the components of the aqueous shunt should be essentially free from pits, scratches, cracking and crazing at a minimum of 6x magnification. The edges of the shunt should appear smooth and free of

burrs and flash when inspected at 6x magnification. The overall dimensions of the aqueous shunt and the dimensions of the drainage area in terms of thickness, length and width should be within ± 5% of the design nominal. The inlet and discharge tubes should have an outer diameter and inner diameter within 15% of design nominal.

III. Clinical Data

Clinical data are needed in each 510(k) to confirm the clinical performance of the aqueous shunt. Aqueous shunts are considered significant risk devices, and clinical investigations performed in the United States must take place under an investigational device exemptions (IDE). Aqueous shunts that have a long history of clinical usage may be able to satisfy this recommendation with published clinical studies that demonstrate the safety and effectiveness of the device.

New aqueous shunts (i.e., new materials, new designs) should be evaluated with a clinical investigation developed with the protocol elements provided in Appendix C or an equivalent protocol which has similar statistical power to detect clinically significant differences between the test and the control populations.

IV. Examples of Predicate Devices

Krupin Eye Valve	K885125 and K905703
Molteno Implant	K890598 and K902489
Glaucoma Pressure Regulator	K903462
Baerveldt Glaucoma Implant	K905129 and K955455
Ahmed Glaucoma Valve Implant	K925636

V. Sterilization Information

The method used to sterilize the device should be validated using a method appropriate for the sterilization method. The test methods specified below are suggested methods. Alternative methods are permitted if appropriately validated.

The recommendations for sterilization outlined in FDA's ODE Guidance Memorandum #K90-1 should be evaluated for sterile devices. The aqueous shunt should be provided sterile. Whenever possible, the product should be terminally sterilized in its final container. However, if the device is provided non-sterile, the ODE Guidance "Labeling of Reusable Medical Devices for Reprocessing in Health Care Facilities: FDA Reviewer Guidance" should be consulted and the issues identified and addressed.

A. Steam Sterilization

Validation of steam sterilization should be carried out in accordance with the requirements of ANSI/AAMI/ISO 11134-1993 (Sterilization of health care products -- Requirements for validation and routine control -- Industrial moist heat sterilization).

B. Ethylene Oxide (EO) Sterilization

Validation of EO sterilization should be carried out in accordance with the requirements of ANSI/AAMI/ISO 11135-1994 (Medical devices -- Validation and routine control of ethylene oxide sterilization).

EO residual testing should be carried out in accordance with ISO 10993-7 (1995) (Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals) with the following modifications:

- The procedure should consist of a solvent exhaustive extraction or a headspace exhaustive extraction.

  Note - Sponsors should choose a solvent that adequately swells or dissolves the aqueous shunt material to facilitate extraction of the EO molecules. A headspace method may be used if it has been validated to demonstrate that the extraction is as exhaustive as a solvent method. Alternatively, a sponsor may demonstrate the relative efficiency of an extraction method and adjust the internal release specifications accordingly.

- The ethylene chlorohydrin (ECH) residue in aqueous shunts should not exceed 2.0 µg ECH per device per day, not to exceed 5.0 µg per device.

Note - Ethylene glycol residues should be sufficiently controlled by the limits set for EO and ECH residues.

Alternatively, the methods described in AAMI ST29-1988 (Recommended practice for determining residual ethylene oxide in medical devices) may be used with the following specified limits:

Residue	**Limit**
Ethylene oxide	25 ppm
Ethylene chlorohydrin	25 ppm
Ethylene glycol	500 ppm

C. Radiation Sterilization

Validation of radiation sterilization should be carried out in accordance with the requirements of ANSI/AAMI/ISO 11137 (Sterilization of health care products -- Requirements for validation and routine control -- Radiation sterilization).

VI. Packaging and Labeling

A. Packaging: The packaging is intended to provide adequate protection to the aqueous shunt from damage during shipping and maintain the sterility of the device for the duration of its shelf-life. Therefore, the following information should be submitted:

a. A description of the packaging, including the packaging materials and the configuration of the final packaged product should be provided.

b. The sponsor should demonstrate that the package maintains the sterility of the device for the duration of the proposed shelf life. A validated seal integrity test in combination with a validated microbial barrier test of the packaging material(s) or a validated whole package physical integrity test should be performed on the finished product before and after aging. Examples of such testing may be found in ISO 11607 (Packaging for terminally sterilized medical devices).

FDA prefers real-time aging be performed for establishing shelf life; however, accelerated aging up to 5 years may be acceptable for device materials with a history of use in ocular implants (e.g., polymethylmethacrylate (PMMA)) and for package materials with a history of use in similar sterilization conditions (e.g., Tyvek pouches sterilized with 100% EO).

B. Labeling: The labeling for the aqueous shunt should contain the following:

- Name of manufacturer
- Trade name of the product
- A description (materials) and diagram (including top and side views) of the device which contains its dimensions (including the maximum thickness, length and width of both the overall device, the drainage area, and the explant surface area)
- Lot/batch number
- Indications for use
- Instructions for use
- Clinical results (including adverse events)
- Warning that the device is sterilized until opened
- Precautions to be taken for handling and safe use

- Statement that the device is for single use only

Definitions provided in ODE Guidance Memorandum #G91-1 should be referenced when necessary. The labeling requirements described in 21 CFR Part 801 also apply.

Appendix A
(informative)

Recommended standard practices for in-vitro flow characterization of aqueous shunts

A.1 Gravity Flow Test

A.1.1 Purpose

The purpose of this test is to evaluate the pressure/flow characteristics of an aqueous shunt when exposed to a decreasing pressure gradient in an aqueous environment. The experimental data obtained from this test may be used to calculate a theoretical resistance to flow for the aqueous shunt.

A.1.2 Study Design

A minimum of five finished aqueous shunts (randomly chosen) should be used (from separate lots, if available).

A.1.3 Test Material

The aqueous shunts should be fabricated according to intended production methods, and be the same as those used in clinical studies.

A.1.4 Materials and Equipment

-T-connector
-3-way valve
-Pressure transducer
-Manometer (may be assembled by attaching a cylinder vertically to a ring-stand)
-Tubing
-Syringe
-Deaerated, distilled water
-Water bath (35°C) in reservoir
-27-gauge cannula (or other as necessary)
-Clamp

A.1.5 Set-up

Insert cannula into drainage tube of aqueous shunt. Prime test samples prior to testing by wetting all internal surfaces (for valved devices, the valve should be primed by opening the valve) by injecting water into shunt through a syringe. Check for leaks. The aqueous shunt is placed in water bath for at least one hour prior to testing to assure stable pressure/ flow characteristic. Connect cannula of aqueous shunt to syringe and tubing via a 3-way valve. The manometer is

connected via a t-connector to the pressure transducer and the tubing to the aqueous shunt. Fill system from syringe with water, ensuring that no air bubbles are present in the system. System should be filled so that the initial pressure that the shunt is exposed to at least 40 mmHg. This allows for a recording of a large enough range of pressure data for calculations. Isolate manometer from system with the clamp. Adjust level of water bath until surface is level with the pressure transducer and the pressure reading is zero mmHg. The reservoir for the water bath should be large enough such that any changes in the surface level result in negligible effects on the pressure. Isolate syringe from system at 3-way valve. Remove clamp. Record pressure and time as fluid drains through shunt. Stop recording data when pressure readings are steady (within +/- 0.3 mmHg) for several minutes.

A.1.6 Evaluation of Data

Conservation of mass dictates that the flow, Q, through the device can be calculated by recording the change in volume over time:

$$Q(t) = A\, dh/dt,$$

where A is the constant cross-sectional area of the gravity feed tube and h is the height of the saline in the tube that is changing over time. Pressure, P, can be calculated from fluid height by

$$P = \rho g h,$$

where ρ is the density of the fluid and g is gravity. The equation for flow then becomes

$$Q(t) = (A/\rho g)\, dP/dt.$$

Therefore, the measurement of pressure over time, P(t), may be used to calculate the flow over time, Q(t). Define resistance to fluid flow, R, (analogous to electrical resistance) as

$$R = P/Q,$$

where P is the pressure drop between two points in a pipe and Q is the fluid flow that results. The resistance of an aqueous shunt will depend on various characteristics of the shunt, including drainage tube material (and its flexibility), flow restrictor design, and characteristics of the attachment of the drainage tube to the explant. Solving for P and inserting into the equation for flow results in a differential equation for pressure for which the solution can be expressed as an exponential of the following form:

$$P = a\, e^{-bt} + c.$$

The pressure versus time data obtained can be fit to an exponential curve. Once the equation of this curve is obtained, the flow, Q, can be calculated from dP/dt, and plotted against the pressure. The slope of the line resulting from this plot is the resistance. The resistance calculated from this plot will be the resistance of the testing apparatus and cannula as well as that of the shunt. Therefore, since resistance is additive in series, testing should be performed with the cannula attached to the testing apparatus to obtain the resistance of the testing apparatus and cannula. The resistance of the shunt is obtained by the following:

$$R_{implant} = R_{total} - R_{system\ +\ cannula}.$$

A.2 Constant Flow Test

A.2.1 Purpose

The purpose of this test is to evaluate the pressure/flow characteristics of an aqueous shunt when exposed to a constant flow rate (mimicking physiological flow rates) in an aqueous environment. The experimental data obtained from this test may be used to calculate a theoretical resistance to flow for the aqueous shunt. Additionally, the opening pressure of a valved shunt can be obtained from this test method.

A.2.2 Study Design

A minimum of five finished aqueous shunts (randomly chosen) should be used (from separate lots, if available).

A.2.3 Test Material

The aqueous shunts should be fabricated according to intended production methods, and be the same as those used in clinical studies.

A.2.4 Materials and Equipment

-T-connector
-Pressure transducer
-Variable-speed pump
-Tubing
-Syringe
-Deaerated, distilled water
-Water bath (35°C) in reservoir
-27-gauge cannula (or other as necessary)

A.2.5 Set-up

Insert cannula into drainage tube of aqueous shunt. Prime test samples prior to testing by wetting all internal surfaces (for valved devices, the valve should be primed by opening the valve) by injecting water into shunt through a syringe. Check for leaks. The aqueous shunt is placed in water bath for at least one hour prior to testing to assure stable pressure/ flow characteristic. Connect cannula of aqueous shunt to syringe pump and pressure transducer via a t-connector and required tubing. Using fluid filled syringe from syringe pump, inject fluid into the testing system and assure that there are no air bubbles present. Adjust level of water bath until surface is level with the pressure transducer and the pressure reading is zero mmHg. The reservoir for the water bath should be large enough such that any changes in the surface level result in negligible effects on the pressure. Adjust the pump speed to provide a flow rate of 2 µl/minute. Record pressure after stabilization. For valved devices, record pressure peak at which valve opens and subsequent

stabilization pressure. Repeat flow experiment with at least five flow rates ranging between 0.5 µl/minute to 5 µl/minute.

A.2.6 Evaluation of Data

Plot the average of the results obtained from the two devices (indicate individual data points for discrepancies) with flow on the horizontal axis and pressure on the vertical axis. Fit a regression line to the plotted data and report the r-value (the measure of how well the data meets the regression line). Report the resistance as the slope of the line. As discussed above, the resistance of the testing system without the shunt should be deducted from the results to obtain the resistance of the shunt.

For a valved shunt, an opening pressure should be evidenced by a pressure peak. Report the average and standard deviation of the opening pressure for the five flow rates. If a closing pressure is noted during testing, this value should be reported also.

A.3 Valve Open/ Close Pressures Test

A.3.1 Purpose

The purpose of this test is to evaluate the pressures at which the valve of a valved aqueous shunt will open and close in an aqueous environment.

A.3.2 Study Design

A minimum of five finished aqueous shunts (randomly chosen) should be used (from separate lots, if available).

A.3.3 Test Material

The aqueous shunts should be fabricated according to intended production methods, and be the same as those used in clinical studies.

A.3.4 Materials and Equipment

-T-connector
-Pressure transducer
-Tubing
-Hand pump
-Deaerated, distilled water
-27-gauge cannula (or other as necessary)
-Syringe

A.3.5 Set-up

Insert cannula into drainage tube of aqueous shunt. Prime test samples prior to testing by wetting all internal surfaces (for valved devices, the valve should be primed by opening the valve) by injecting water into shunt through a syringe. Check for leaks. Connect cannula to tubing and pressure transducer via t-connector. Fill tubing with water. Calibrate pressure transducer to indicate zero at the point where fluid fails to flow from the tip of the cannula. Insert cannula into drainage tube of shunt. Gently increase the pressure in the device using the hand pump until fluid flows through the valve of the shunt. Increase pressure to a value around 100 mmHg to check for continuous flow through the valve. Slowly reduce pressure while intermittently blotting fluid from the explant until all flow is observed to stop for a period of 30 seconds. Record the closing pressure. Gradually increase pressure until fluid flows through the valve for a period of 30 seconds. Record the opening pressure. Repeat five times with same device and average.

A.3.6 Evaluation of Data

The average opening and closing pressures for each of the two samples should be reported.

Appendix B
(informative)

Recommended standard practices for biocompatibility testing of aqueous shunts

B.1 Ocular implant study (six months) with pathology

A subcommittee of the American National Standards Institute (ANSI) Z80 Committee is currently in the process of developing a standard that includes this test method.

B.1.1 Purpose

The purpose of this test is to evaluate the biocompatibility of an aqueous shunt material in an ocular environment by surgical implantation in the eye of an appropriate animal model for six months. This test serves to assess the suitability of the shunt material and design for human clinical use.

B.1.2 Rationale for the selection of the animal model

Historically, several animal species have been used for this test including rabbits, cats, and primates (usually the cynomolgus or rhesus monkey). The rationale for the choice of animal is based on the experimental question(s) being considered, and therefore the scientific judgment of the investigator is important. The choice of animal model should be appropriate to answer all of the theoretical concerns relating to the biocompatibility of the material including, but not limited to the following:
- inflammatory response of the eye (both implanting and fellow eye) to the material;
- adhesion of cells to the surface of the implant;
- biodegradation of the implant material(s).

B.1.3 Study design

A minimum number of animals should be used, such that a minimum of six tests are available at the end of the six-month period. One eye in each of the animals will be implanted with the test shunt. The treated eyes will be monitored by slit lamp biomicroscopy and indirect ophthalmoscopy for up to 6 months. The minimum of six tests should be followed for six months to be considered a valid test.

B.1.4 Test material

The aqueous shunt material should be fabricated into an aqueous shunt according to intended production methods. To allow for dimensional differences between human and animal eyes, the explant might require custom design to fit the anatomical placement site.

B.1.5 Materials and equipment

- Operating microscope;
- Slit lamp;
- Indirect ophthalmoscope;

- Lid speculum;
- Beaver blades;
- Balanced Salt Solution, Sterile (BSS);
- Ketamine;
- Antibiotic steroid ointment.

B.1.6 Animals

The animals will be acquired from approved vendors in accordance with the requirements of the Animal Welfare Act. Animals of either sex can be used as long as the sex is identified in the records. They are to be housed in a facility fully accredited by the American Association for Accreditation of Laboratory Animal Care. Each animal will be tattooed and individually housed for identification purposes. All animals will be subjected to slit lamp biomicroscopy and indirect ophthalmoscopy prior to use and animals with any ocular abnormalities will be rejected. The animals are to be fasted the day before surgery and weighed prior to use. The animals will be given appropriate food and water ad libitum during the course of the study.

B.1.7 Surgery

The surgical techniques and intraoperative and postoperative regimen should be those appropriate for the particular animal used as determined by the surgeon based on his/her experience. The following describes briefly a generalized method.

The animal is anesthetized with an intramuscular injection of a combination drug containing ketamine. The animal is then placed on the operating table and draped. Procedures are done under an operating microscope using aseptic techniques.

After insertion of a lid speculum, a fornix-based conjunctival flap is dissected between the insertion of two adjacent rectus muscles. The shunt explant is sutured to the sclera an appropriate distance posterior to the limbus. The shunt tube is inserted into the anterior chamber through an appropriate-sized needle tract (typically 23-gauge). A patch graft may be placed over the anterior portion of the tube. The conjunctival wound is closed and an antibiotic/steroid ointment is applied to the eye. The animal is returned to its cage.

Intraoperative observations should include the following:
- tube/material and endothelium touch;
- collapse of the anterior chamber;
- significant anterior chamber bleeding;
- iris damage;
- placement of the shunt explant and tube, where applicable;
- excessive fibrin formation;
- unusual surgical problems that are not common to the group as a whole

B.1.8 Postoperative evaluations

The operated eyes will be grossly examined at days 1 and 3. Slit lamp biomicroscopy and indirect ophthalmoscopy will be performed at 7 days, 4 weeks, and at months 3 and 6. Observations should include, but not be limited to, flare, cells, adhesions, neovascularization, corneal edema, location of the tube and explant, where applicable. These examinations can be carried out more often if needed.

B.1.9 Evaluation of explanted eyes

The animals will be sacrificed at the end of their respective follow-up periods and the eyes enucleated. The eyes of any animals that die during the course of the study other than from surgical trauma or complications should also be evaluated. A minimum of three of the enucleated eyes should be immersed immediately in neutral buffered formalin for fixation and storage. The retrieved eyes will be sectioned equatorially and an internal examination performed. Any visible abnormalities and the location/placement of the implant is noted, and photographs taken. Histopathological evaluations will be performed on the anterior and posterior segments of the eye by an ophthalmic or a veterinary pathologist.

B.1.10 Evaluation of explanted shunts

The shunts should be examined for cellular and fibrinous deposits as well as other abnormalities, particularly at the tube/explant junctions and inside the tubes, where applicable. Photographs should be taken at appropriate magnifications to document findings. A minimum of two shunts that have been implanted for six months should be submitted for pressure/flow testing after the cellular debris is carefully removed. Following pressure/flow testing, the structural integrity of the shunts should be tested.

B.1.11 Interpretation of results

The clinical results and histological data obtained for the test group should be evaluated for biocompatibility and physical properties. The aqueous shunt material will be judged biocompatible if placement of this material in the animal eye does not elicit a significant response clinically or histologically, and if there is no detectable change in the flow properties.

Appendix C
(informative)

Recommended standard practice for the clinical evaluation of aqueous shunts

C.1 Aqueous shunt clinical protocol elements

The following are important elements of a clinical protocol which will assist the sponsor in collecting sufficient, relevant and appropriate data to determine the safety and effectiveness of aqueous shunts which are within the scope of this guidance. These elements were derived from the clinical experience with these devices, beginning in 1977 (Krupin-Denver and Molteno).

C.1.1 Control population

The clinical performance of the aqueous shunt under investigation should either be compared to an appropriate historical population with an appropriate methodology or to the results of a concurrently run control population. The sponsor should be aware that clinical performance levels for a large historical control population have never been established.

C.1.2 Number of subjects

The clinical investigation should include a minimum of 50 subjects with one-year follow-up. The performance of the aqueous shunt will be compared to the performance of either the historical control or a concurrently studied control. The sponsor should strive to use an historical population with at least 50 subjects or as large as possible so that the rates of adverse events and changes in intraocular pressure (IOP) are as close as possible to the true rates for the indicated population. For optimal clinical comparison of the aqueous shunt to an appropriate, concurrently studied control population, the sponsor should enroll a minimum of 50 subjects per study arm to evaluate changes in IOP and adverse events. Expert help with study design and statistical analysis is essential. The sponsor should be aware that any additional claims beyond the safety and effectiveness of the aqueous shunt may require the calculation of an appropriate sample size in all cases. Study design should allow for subjects lost to follow-up during the clinical investigation. The sponsor should refrain from enrolling significantly larger numbers of subjects than originally planned to minimize the number of subjects which are exposed to the risks associated with the implantation of an aqueous shunt model which has not yet been determined to be safe and effective.

To assist in achieving a balance in the number of subjects from each investigator in multi-center trials, the sponsor's clinical protocol should state that each surgeon/investigator enroll a minimum of 5 subjects, and no more than 25% of the total subjects in the investigation. Each center should not enroll more than 33% of the total subjects in the investigation.

C.1.3 Duration of the clinical investigation

The follow-up duration of the clinical investigation should be at least one-year.

C.1.4 Reporting periods

As a minimum, the clinical data for the subjects should include the postoperative reporting forms up to Form 4 for a one-year clinical investigation:

Form 0: Preoperative/Operative reporting
Form 1: Postoperative reporting 1-3 days postoperatively
Form 2: Postoperative reporting 7-35 days postoperatively
Form 3: Postoperative reporting 150-210 days postoperatively
Form 4: Postoperative reporting 330-420 days postoperatively

Unscheduled visits and the procedures to capture adverse events that may occur between reporting forms should be addressed in the investigation plan. IOP should be reported at each reporting form; additionally, IOPs between forms should be recorded (if reported).

C.2 Clinical data collection and analysis

Additional clinical guidance which will assist the sponsor in designing their aqueous shunt clinical investigation protocol and in analyzing the data from that investigation is listed below.

C.2.1 Standardization of the clinical evaluation

The sponsor should ensure to the extent possible that the criteria used by all investigators for evaluation of adverse events, and the parameters associated with IOP, visual acuity, and visual field examinations (if performed) conform to the standards recommended by the National Eye Institute (Eye Care Technology Forum Recommendations).

C.2.2 Adverse Events

Any undesirable clinical occurrence in a subject whether it is considered to be device related or not should be reported. Adverse events may be intraoperative or postoperative. The following adverse events are recommended to be included as forced-choice items on your clinical report forms.

Intraoperative adverse events:

- Device malfunction identified prior to implantation;
- Inadvertent perforation of sclera;
- Hyphema;
- Inadvertent loss of vitreous; and
- Choroidal hemorrhage or effusion.

Postoperative adverse events:

- Flat anterior chamber (central lens, corneal touch);
- Visual acuity loss (loss of two Snellen lines or more, or loss of light perception; no light perception is always reportable; beyond 20/400, the increments corresponding to one line are as follows: 5/200, 2/200, 1/200, hand movement, and light perception);
- Tube malposition;
- Device malfunction (including presumed tube compression/kink);
- Tube insertion within choroid (for pars plana);
- Tube and/or flow restrictor obstruction by iris, vitreous, lens, fibrous overgrowth, fibrin, blood, etc.;
- Unintended implant exposure (including tube);
- Wound dehiscence (persistent aqueous leak or fistula formation);
- Inflammation (persistent at 6 months and non-preexisting anterior or posterior uveitis in same or fellow eye, sterile hypopyon, or pupillary membrane formation);
- Infection (localized to area of device or endophthalmitis);
- Bleeding (vitreous hemorrhage or persistent and non-preexisting hyphema);
- Corneal complications (corneal edema, opacification, or graft decompensation);
- Cataract (formation or progression);
- Retinal complications (dialysis, flap tears, retinal detachment, or proliferative vitreoretinopathy);
- Choroidal complications (massive choroidal hemorrhage);
- Strabismus (any new restriction of ocular movement or secondary diplopia);
- Unplanned surgical reintervention;
- Loss of eye;
- Chronic pain;
- Ptosis; and
- Atrophy/phthisis.

C.2.3 Guidance on data analysis

The sponsor should consider the following clinical data analyses:

- IOP vs. medications at each visit (Goldmann applanation or equivalent);
- IOP and VA by preoperative ocular pathology;
- VA by amount of change (i.e., within one line, increase of two lines or more, and decrease of two lines or more with explanation);
- rates of cumulative and persistent adverse events;
- rates of other (undefined in this document) adverse events;
- IOP by investigator; and
- rates of adverse events by investigator.

This clinical data evaluation should demonstrate whether or not an aqueous shunt's failure to meet the clinical performance levels associated with historical or concurrent control populations is device related.

Although rates of all adverse events should be reported, rates for the following should be compared to those from the control population: aqueous shunt malfunction identified prior to or during implantation (such as inability to irrigate through with a syringe, leaks, etc.); massive choroidal hemorrhage; unplanned surgical reintervention; visual loss at six months; unintended implant (including tube) exposure; infection; flat anterior chamber; persistent severe inflammation (sterile hypopyon or pupillary membrane formation); and aqueous shunt malfunction postoperatively.