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Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

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For questions about this document, contact the Division of Ophthalmic and Ear, Nose, and Throat Devices (DOED) at 301-796-5620.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Ophthalmic and Ear, Nose, and Throat Devices
Intraocular and Corneal Implants Branch

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Preface

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Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices

Draft Guidance for Industry and Food and Drug Administration Staff

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I. Introduction

When finalized, this draft guidance document will recommend non-clinical and clinical studies to support a premarket approval (PMA) for implantable minimally-invasive glaucoma surgical (MIGS) devices. Glaucoma is a progressive condition that damages the optic nerve of the eye, is associated with elevated intraocular pressure, and leads to irreversible vision loss. It is the second leading cause of visual disability and blindness in the world, with 1 in 40 adults over 40 years of age suffering from glaucoma having some visual loss.[1,2] Current treatments for glaucoma are designed to reduce the intraocular pressure (IOP). Many options are available to lower the IOP including medications, laser treatments, and surgical interventions. Current surgical treatments for glaucoma are aimed at reducing intraocular pressure through the reduction of aqueous inflow or the enhancement of aqueous outflow. While trabeculectomy is the standard surgical intervention for glaucoma, it is often reserved for moderate to severe disease. During the past decade, novel medical devices, called MIGS devices, have emerged. These devices are designed to treat less severe glaucoma by enhancing physiological aqueous outflow with an approach that causes minimal ocular trauma.

This guidance represents the Agency's initial thinking and our recommendations may change as more information becomes available. The Agency strongly encourages manufacturers to engage with CDRH through the Pre-Submission process to obtain more detailed feedback for implantable MIGS devices. For more information on Pre-Submissions, please see "Requests for

Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Scope

The recommendations made in this draft guidance are applicable to implantable MIGS devices, a type of Intraocular Pressure Lowering Device (associated with product code OGO) used to lower intraocular pressure using an outflow mechanism with either an *ab interno* or *ab externo* approach and associated with little or no scleral dissection and minimal or no conjunctival manipulation. Intraocular Pressure Lowering Devices are Class III devices and are defined as devices intended to reduce intraocular pressure when implanted in eyes which have not failed conventional medical and surgical treatment.

The recommendations in this guidance document do not apply to implants used to reduce IOP in the anterior chamber of the eye in patients with neovascular glaucoma or with glaucoma when medical or conventional surgical treatments have failed, associated with product code (KYF) and regulated as class II devices under 21 CFR 886.3920, Aqueous Shunt.

III. Definitions

For purposes of this guidance document, the following definitions apply:

Glaucoma: An ophthalmic disease usually characterized by increased intraocular pressure (IOP) resulting in damage to the optic nerve and documented by typical visual field defects.

Humphrey Visual Field (HVF): Standard automated test method to measure full extent of the area visible to an eye that is fixating straight ahead and is measured in degrees from fixation. During this test, lights of varying intensities are presented in different parts of the visual field while the subject focuses on one spot. The perception of these lights is charted.

Hypotony: An intraocular pressure (IOP) less than 6mm Hg.

Intraocular Pressure (IOP): Assessment of pressure in the eye with a tonometer. It is measured in millimeters of mercury (mmHg).

IOP Lowering Device: A device intended to reduce IOP when implanted in eyes that have not failed conventional medical and surgical treatment.

Hypotony Maculopathy: Abnormality of the macula in the setting of hypotony characterized by optic nerve head swelling, tortuous blood vessels, and chorioretinal folds.

Glaucoma Hemifield Test: A particular analysis of the HVF that compares points in the upper field to corresponding points in the lower field and then interprets the results as (a) "outside normal limits" indicating the upper and lower fields are different and may signify glaucoma, (b) borderline, and (c) within normal limits indicating glaucoma may not be present.

Mean Deviation (MD): Average of the deviation for each point on the visual field when compared with age-matched controls.

Minimally-Invasive Glaucoma Surgical (MIGS) Device: A type of IOP Lowering Device used to lower IOP using an outflow mechanism with either an *ab interno* or *ab externo* approach, associated with little or no scleral dissection and minimal or no conjunctival manipulation.

Ocular Hypertension: A condition with elevated IOP but no signs of visual field loss or optic nerve damage associated with glaucoma. These subjects are also called "glaucoma suspects."

Pattern Deviation (PD) Plot: This measure from the automated visual field provides information about localized defects by adjusting for generalized visual field loss due to other factors like media opacity (e.g., cataract or a vitreous hemorrhage).

Washout: Part of a clinical trial when a subject is asked to stop taking all medications. This can occur prior to initiating the investigational treatment as well as before assessing clinical endpoints.

IV. Non-Clinical Testing Recommendations

All non-clinical testing should be performed on the finished sterilized product that is intended to be marketed.

A. Biocompatibility Testing

If the actual device cannot be used in testing (e.g., due to the small area of the device), test samples (e.g., coupons) that are representative of the final device may be employed for biocompatibility testing.

1. Recommended Biocompatibility Tests

The following tests should be performed as recommended by Bluebook Memorandum G95-1 Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm).

a. Cytotoxicity
b. Sensitization
c. Ocular irritation
d. Systemic toxicity (acute toxicity)
e. Sub-chronic toxicity (subacute toxicity)
f. Genotoxicity
g. Carcinogenicity
h. Pyrogens Testing. If the device contacts blood then material-mediated pyrogenicity testing is also recommended.

In addition, ocular implantation testing should be conducted as outlined in Annex B of the most current, FDA-recognized version of the American National Standards Institute (ANSI) Z80.27 "American National Standard for Ophthalmics – Implantable Glaucoma Devices." There might be cases (e.g., inflammation) in which the 6-month implantation study recommended in ANSI Z80.27 is not sufficient and longer implantation studies may be needed.

2. Recommended Physico-Chemical Tests

a. Test of Extractables and Hydrolytic Stability: Testing should be conducted as outlined in Annex C of the most recent, FDA-recognized version of ISO 11979-5 "Ophthalmic Implants – Intraocular Lenses – Part 5: Biocompatibility."
b. Test of Extractables by Exhaustive Extraction (Annex C of ISO 11979-5)
c. Leachables (Annex D of ISO 11979-5)
d. Insoluble Inorganics (ISO 11979-5)

3. Bioabsorbable Materials

This testing should be performed if the material is in situ polymerizing and bioabsorbable.

Toxicity should be assessed for the finished product as well as at various time points over the course of polymerization and/or degradation to ensure that starting, intermediate and final degradation products are evaluated. Assessments should continue until the polymer is no longer present in the tissue, or until the biological tissue response is demonstrated to be stable.

4. Biological Response from Device Mechanical Failure

For devices incorporating a coating or multiple material components, it is possible that mechanical failure could alter the biological response to the device. For devices with the potential for biological hazard due to mechanical failure, the biocompatibility testing should include testing to address this concern.

5. Sample Preparation

For biocompatibility testing using extracts of samples, the extraction should be conducted using both polar (water, physiological saline) and non-polar (sesame oil, cotton oil) extraction vehicles under conditions as described in the most recent, FDA-recognized version of International Organization for Standardization (ISO) 10993-12 "Biological evaluation of medical devices -- Part 12: Sample preparation and reference materials." For permanently implanted devices, extraction at 37°C for 72 hours may not be sufficient to obtain an extract that represents the chemicals that may leach out over the use life of the device. However, in some cases, temperatures over 37°C may result in degradants and toxicities that are not representative of the device. Therefore, a justification for the selected extraction conditions should be provided.

Extraction should be performed based on surface area of the device. If the area cannot be determined than a mass/volume should be used. The test extract should not be processed (e.g., filtered or centrifuged) and should be used immediately after preparation.

Extraction in tissue culture media supplemented with serum is acceptable for cytotoxicity testing and should be performed according to the most recent, FDA-recognized version of ISO 10993-5 "Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity."

A scientifically-based rationale for omission of any recommended test should be included with the submission. We recommend that sponsors who do not intend to conduct biocompatibility testing submit a pre-submission to obtain feedback from the Division of Ophthalmic and Ear, Nose, and Throat Devices on the their rationale. For more information on Pre-Submissions, please see "Medical Devices: The Pre-Submission Program and Meetings with FDA Staff"

(http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf).

B. Physical and Mechanical Testing

Device properties should be determined at *in situ* conditions with the temperature tolerance of ± 2 °C. The precise composition of the solution used should be reported in all cases. FDA recommends that testing be conducted as outlined in Physical and Mechanical Testing of Section 5 of ANSI Z80.27 with the following additions and exceptions.

1. Validation of Dimensional Tolerances

(Section 5.4 of ANSI Z80.27) Dimensions for which tolerances are given should be specified in the manufacturer's design documentation. The sponsor should validate that their production meets their tolerances to appropriate statistical levels.

2. Surface and Edge Quality

(Sections 5.2 and 5.3 of ANSI Z80.27) The device should be essentially free from surface defects and all edges should appear smooth when viewed at 10x magnification with a stereo microscope using optimal lighting conditions. Any questionable or critical areas should be viewed at higher magnification.

3. Structural Integrity

(Section 5.7 of ANSI Z80.27) The manufacturer should provide evidence that the device can withstand surgical manipulations without failure. An appropriate test method and specification should be established by the manufacturer to ensure that the device does not fail at typical deformations.

4. Insertion Testing

The purpose of this testing is to evaluate the integrity of the delivery system and of the delivered device, if the MIGS device is designed to be delivered from an injector system. The injector system should be evaluated following the instructions supplied by the manufacturer and using recommended lubricants and instrumentation. There should be no change in the physical properties of the MIGS device and no damage to the injector system as a result of the delivery. The results should be reported and are acceptable if the physical properties of the MIGS device remain within manufacturing specifications of the product.

5. Coated Devices

MIGS devices with surface coatings should conduct testing per Section 9.2 of ANSI Z80.27.

6. Metallic Devices

MIGS devices manufactured with metallic materials should be evaluated for Magnetic Resonance Imaging (MRI) safety according to "FDA Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM107708.pdf) and for corrosion resistance according to the most recent, FDA-recognized version of ASTM F2129 "Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices."

C. Sterility and Package Integrity

1. Sterilization Method

The sterilization method should be validated according to one of the following standards:

a. For moist heat (steam), use the most recent, FDA-recognized version of ANSI/AAMI/ISO 17665-1 "Sterilization of Health Care Products – Moist Heat – Part 1: Requirements for the Development, Validation, and Routine Control of a Sterilization Process for Medical Devices."

b. For ethylene oxide, use the most recent, FDA-recognized version of ISO 11135 "Sterilization of Health Care Products – Ethylene Oxide – Requirements for the Development, Validation, and Routine Control of a Sterilization Process for Medical Devices."

c. For gamma radiation, use the most recent, FDA-recognized version of ANSI/AAMI/ISO 11137-1 "Sterilization of Health Care Products – Radiation – Part 1: Requirements for the Development, Validation, and Routine Control of a Sterilization Process for Medical Devices."

2. Ethylene Oxide Sterilant Residues

If the MIGS device is sterilized via ethylene oxide, then the maximum

level of ethylene oxide residuals that remain on the device should be quantified and assessed according to the most recent, FDA-recognized version of ISO 10993-7 "Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals." An exhaustive solvent or head space extraction method should be chosen and the amount of residue should conform to those for intraocular lenses. If the extraction is not exhaustive, release criteria should be lowered in proportion to the relative efficiency of the method.

The residue of ethylene chlorohydrin should not exceed a release of more than 2.0 µg per device per day and not exceed 5.0 µg in total per device.

3. Bacterial Endotoxins

The recommended endotoxin limit for MIGS devices is ≤0.2 EU/device. This limit applies to the segment of the device placed in the anterior chamber and the segment(s) contacting the aqueous humor even though the main portion of the device may reside outside the eye. For devices that have a segment that contacts the aqueous humor and the vitreous or posterior segment, please contact the Division.

4. Package Integrity Testing

Package integrity testing should be performed regardless of the sterilization method and may consist of a validated whole package physical integrity test in combination with a validated seal integrity test. Examples of whole package physical integrity testing can be found in FDA's guidance "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products" (http://www.fda.gov/RegulatoryInformation/Guidances/ucm146074.htm) or the most recent, FDA-recognized version of ANSI/AAMI/ISO 11607-1 "Packaging for Terminally Sterilized Medical Devices – Part 1: Requirements for Materials, Sterile Barrier Systems and Packaging Systems."

D. Shelf Life and Shipping Testing

1. Development of Shelf Life Protocol

The protocol for the shelf life study should be developed prior to initiation of the study. If, during the course of the study, a parameter no longer conforms to the manufacturing specifications at two or more time intervals, the maximum shelf-life of the MIGS device under study has been reached at the last conforming measurement point. If a manufacturer

wishes to maintain the possibility to re-sterilize finished device lots, the finished device lot(s) used in the stability study should undergo the maximum number of sterilization cycles allowed under the manufacturer's procedures. References to suggested test methods can be found in the most recent, FDA-recognized version of ISO 11979-6 "Ophthalmic Implants – Intraocular Lenses – Part 6: Shelf-life and Transport Stability."

2. Real-time Shelf-Life Study

FDA recommends conducting the following stability and integrity studies:

a. Product Stability Studies
- (1) Dimensions
- (2) Surface and Edge Quality
- (3) Structural Integrity
- (4) Pressure/Flow Characterization
- (5) Insertion Testing
- (6) Coating Stability, if applicable

b. Package Integrity Studies
- (1) Whole Package Physical Integrity
- (2) Seal/Closure Integrity

3. Accelerated Shelf-Life Studies

These studies are the same as those performed for real-time shelf life studies with the exception of the conditions in which they are performed. It is important that devices to be measured be allowed to equilibrate to the same conditions as at the initial measurements before being tested. The corresponding real-time shelf-life is calculated by multiplying the studied time period by $2^{(T_a - T_o)/10}$, where T_a is the accelerated temperature and T_o is the typical storage temperature (usually room temperature). The maximum acceptable storage temperature is 45°C. While an initial shelf-life can be established with accelerated testing, a confirmatory real-time shelf-life study should be performed.

4. Transport Stability

The complete, filled device packages (in their normal transport package) should be able to withstand extremes of the temperature and humidity (as expected in shipping), vibration and being dropped. Both the packaging and the product should be inspected following completion of the pre-test conditioning. The device should be considered to have satisfactorily passed the test if the device is free from physical damage when visually inspected under magnification. The packaging should also continue to provide functional protection to the device.

FDA recommends that the following tests be performed, at a minimum:

a. Legibility of Labeling (empty packages can be used);
b. Surface and Edge Quality (sealed packages should be used);
c. Seal/Closure Integrity (empty packages can be used);
d. Whole Package Physical Integrity (empty packages can be used).

V. Clinical Studies

A. Study Design

It is strongly recommended that all subjects be followed for a minimum of 12 months prior to submission of any premarket application, as discussed at the FDA/AGS Workshop on Supporting Innovation for Safe and Effective Minimally Invasive Glaucoma Surgery, February 26, 2014. For additional information, refer to the workshop materials and transcript available on FDA's website at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm382508.htm. For follow-up of less than 24 months, you should provide justification based upon the benefit-risk analysis. For further information on the principal factors FDA considers when making benefit-risk determinations during the premarket review process, please see "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications" (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm267829.htm). If the benefit-risk analysis raises concerns beyond 24 months after implantation, longer follow-up may be appropriate. The investigational plan should include the possibility that long-term follow-up (e.g., up to five years) may be necessary. It is recommended that informed consent for up to five years of follow-up is obtained.

B. Subject Selection Factors

Subjects included in clinical trials for MIGS devices should have evidence of early or moderate open angle glaucoma, which is defined by the following characteristics.

1. Humphrey Visual Field (HVF)

The HVF should be reliable, which is defined as fixation losses, false positives, and false negatives all less than 33%.[4] The following characteristics should also be noted on the HVF:

a. Visual field defects consistent with glaucomatous optic nerve damage;[5] and
b. Mean deviation not worse than -12 dB; and 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."

2. Glaucomatous Optic Nerve Damage

Glaucomatous optic nerve damage as evidenced by any of the following optic disc or retinal nerve fiber layer structural abnormalities:

a. Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles with or without disc hemorrhage;
b. Localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles; or
c. Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue

Subjects that should be excluded from clinical trials for MIGS devices include but are not limited to the following:

1. Subjects who cannot undergo a medication "washout" or who are at high risk for adverse outcomes, including:

a. Subjects on systemic IOP lowering medications.
b. Severe glaucoma defined as mean deviation (MD) of -12.00 to -20.00 and at least one of the following:
(1) 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
(2) At least 50% of points within central 5 degrees with sensitivity of < 0dB; or
(3) Both hemifields containing greater than 50% of points with sensitivity < 15dB within 5 degrees of fixation.
c. End-stage glaucoma defined as glaucoma where the subject is unable to perform HVF using the "worse eye" attributable to a central scotoma from glaucomatous damage OR the "worse eye" visual acuity of 20/200 or less attributable to primary open-angle glaucoma. The "better eye" may be any stage.
d. Fixation-threatening glaucoma: Subjects with visual field defects threatening fixation defined as any (1 or more) point(s) within the central 5° with p value < 5% or worse on PD plot.

2. Subjects with ocular hypertension

3. Subjects at high risk for adverse outcomes due to placing a device in the angle

For details of other subject inclusion and exclusion characteristics (e.g., minimal endothelial cell density), please refer to the non-refractory section of ANSI Z80.27 "American National Standard for Ophthalmics – Implantable Glaucoma Devices."

C. Effectiveness Endpoints

1. Washout

All subjects should undergo a washout period of all IOP-lowering medications prior to surgery to establish a baseline IOP. In addition, if IOP-lowering medications are re-instituted postoperatively, all subjects should undergo a washout period prior to the time point(s) for data collection used in the effectiveness analyses.

2. Primary effectiveness

The recommended primary effectiveness endpoint is the percentage of subjects with reduction of at least 20% (i.e., ≥20%) in mean diurnal IOP from baseline.[6-10] The proposed hypothesis test for the primary effectiveness endpoint should be described in the statistical analysis plan.

3. Secondary effectiveness

The recommended secondary effectiveness endpoint is the mean diurnal IOP change from baseline.

4. Recommended Analyses

In addition to the analyses described in ANSI Z80.27 "American National Standard for Ophthalmics – Implantable Glaucoma Devices," FDA recommends the following additional analyses:

a. Percent Reduction in Mean Diurnal IOP

The number and percent (e.g., n/N & %) of subjects achieving percent reduction (or increase) in mean diurnal IOP at each annual visit from baseline stratified by the percent change in IOP. This analysis should be presented with and without further stratification by baseline mean diurnal IOP.

b. Changes in the Mean, Range, and Maximum of the Diurnal IOP Measurements, and Box-plots of Mean, Range, and Maximum of Diurnal IOP Measurements

Descriptive statistics should be performed as described in ANSI Z80.27 with additional stratification by baseline mean diurnal IOP. Examples of a box-plot can be found in World Glaucoma Association (WGA) Guidelines on design and reporting of glaucoma trials: Consensus on definitions of success – Section II General data presentation requirements.[11]

c. Fluctuation of IOP Measurements Over Time

For each subject, we recommend plotting the diurnal IOP measurements (y-axis) versus time of measurements (x-axis) for baseline and each of the postoperative diurnal IOP visits on the same graph using a different symbol for each visit (See examples in Figures 1 and 2).[11] If applicable, indicate the number of medications the subject is taking on the plot of each visit.

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Figure 1: Dismal IOP at baseline, postoperative month 6 and postoperative month 12 for Patient #32

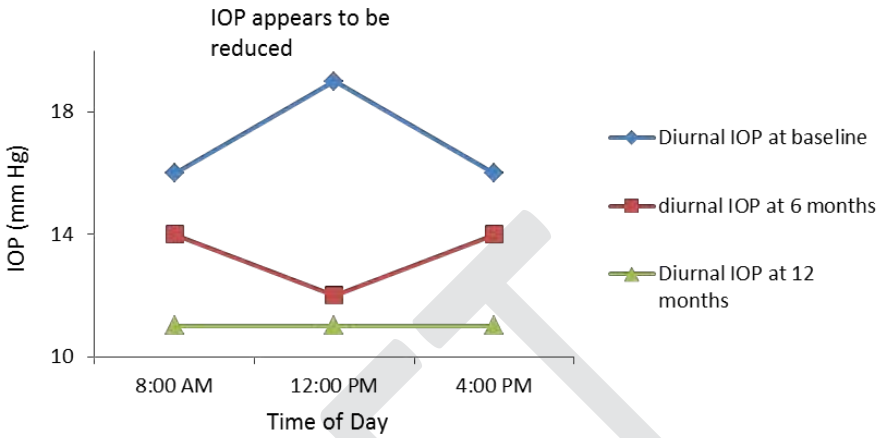
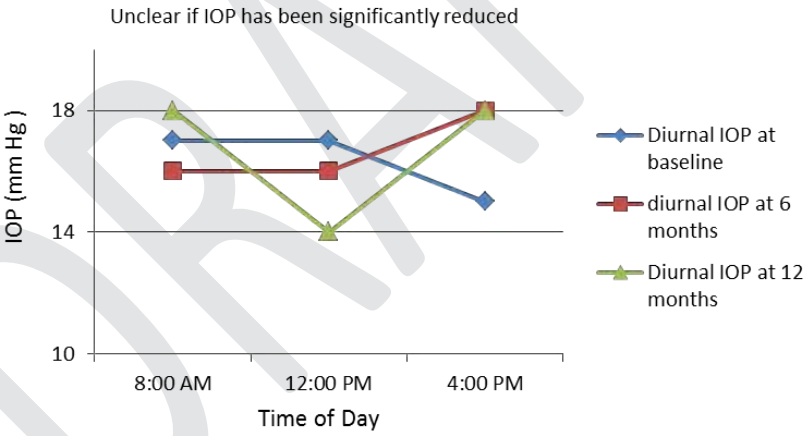


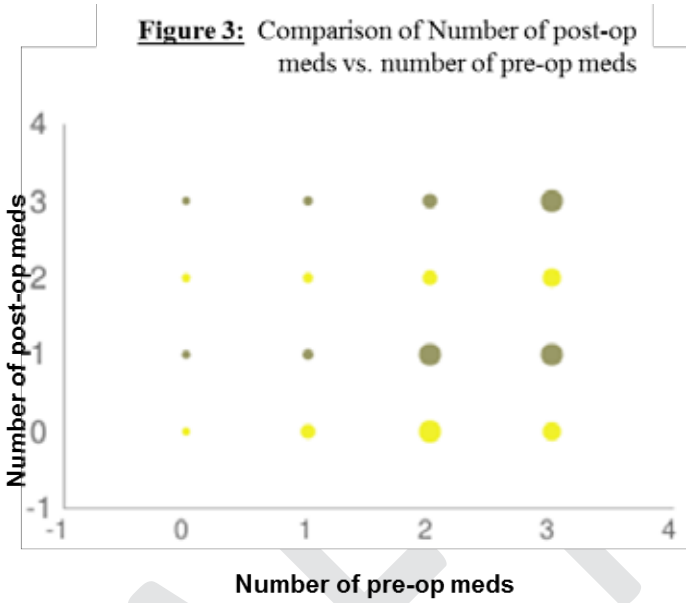
Figure 2: Dismal IOP at baseline, postoperative month 6, and postoperative month 12 for Patient #101



d. Change in Number of Medications

At each postoperative visit, a graphical representation of the number pre-operative (before washout, when applicable) on the x-axis versus post-operative IOP-lowering medications (counting combination drops as separate medications) on the y-axis should be made. An example of such a graphical representation is presented below in Figure 3. The size of each bubble represents the number of subjects.

Figure 3: Comparison of Number of post-op meds vs. number of pre-op meds



e. Assessment of Balance in Baseline Variables

For all studies, we recommend checking for imbalances in baseline variables among the arms of the trial that may affect the outcome (e.g., baseline IOP, age, race, gender, number of medications at screening, etc.).

D. Safety Outcomes

1. The adverse events and device malfunctions for MIGS devices are listed in ANSI Z80.27. The definition of each adverse event should specify the grade or severity, the degree of involvement of the anatomical structure, the timing, and the duration of the event, as applicable, in order to distinguish findings that should be reported as "adverse events" from those observations that should be routinely recorded. Case report forms should include a forced-choice method of recording listed adverse events as well as a method of recording other adverse events not listed.

2. We recommend that hypotony be classified as an early (i.e., at 2 weeks or less following surgery) or late (i.e., more than 2 weeks after surgery) adverse event if it occurs with at least one of the following conditions:

a. Flat anterior chamber requiring anterior chamber reformation
b. Corneal folds
c. Choroidal effusions requiring surgical drainage

d. Suprachoroidal hemorrhage
e. Fluctuating visual acuity
f. Maculopathy
g. Irregular corneal astigmatism
h. Mild glaucoma

3. Substantial visual field loss, compared to baseline preoperative loss, should be defined as at least three, reproducible test points flagged as significantly (e.g., $p<0.05$) progressing at the same locations in pattern deviation-based Glaucoma Change Probability Maps.[12,13]

4. Chronic anterior uveitis should be defined as inflammation of grade 1+ or worse persisting for more than 3 months post-operatively or that recurs less than three months after discontinuing treatment.[14]

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