SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Intraocular Pressure Lowering Implant
Device Trade Name:	iStent *inject* Trabecular Micro-Bypass System (Model G2-M-IS)
Device Procode:	OGO
Applicant's Name and Address:	Glaukos Corporation 229 Avenida Fabricante San Clemente, CA 92672
Date of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P170043

Date of FDA Notice of Approval: June 21, 2018

II. INDICATIONS FOR USE

The iStent *inject* Trabecular Micro-Bypass System (Model G2-M-IS) is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma.

Ill. CONTRAINDICATIONS

The iStent *inject* Trabecular Micro-Bypass System (Model G2-M-IS) (hereafter referred to in this document as iStent *inject*) is contraindicated under the following circumstances or conditions:

- In eyes with angle closure glaucoma
- In eyes with traumatic, malignant, uveitic, or neovascular glaucoma or discernible congenital anomalies of the anterior chamber (AC) angle
- In patients with retrobulbar tumor, thyroid eye disease, Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the iStent *inject* labeling.

V. DEVICE DESCRIPTION

The iStent *inject* contains two preloaded intraocular stents that are manufactured from titanium (Ti6Al4V ELI) and are coated with stearalkonium heparin (note: the heparin is from a porcine source). The stent has a single piece design, is 230 µm in diameter, 360 µm in height, and the central inlet and outlet lumen has a diameter of 80 µm (**Figure 1**). The head of the stent has four side outlets that each have a diameter of 50 µm.

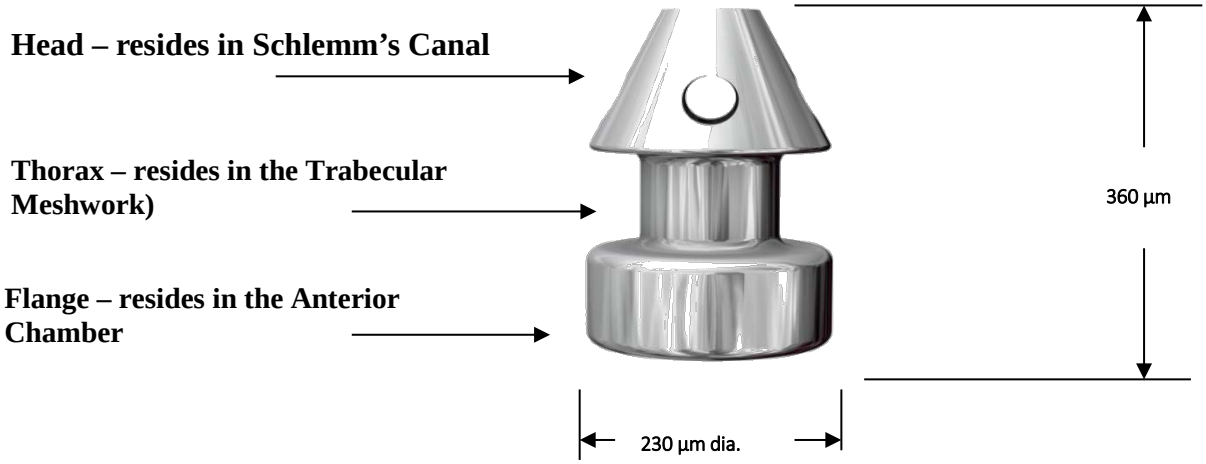

Figure 1. iStent *inject* Stent (Model GTS400) Dimensions

The iStent *inject* stent has a rear flange which resides in the anterior chamber, and a head that resides in Schlemm's canal. The thorax of the stent is retained by the trabecular meshwork. The stent is symmetrical and is designed to be implanted in either the left or right eye (**Figure 2**). Two preloaded intraocular stents are provided in the injector (**Figure 3**).

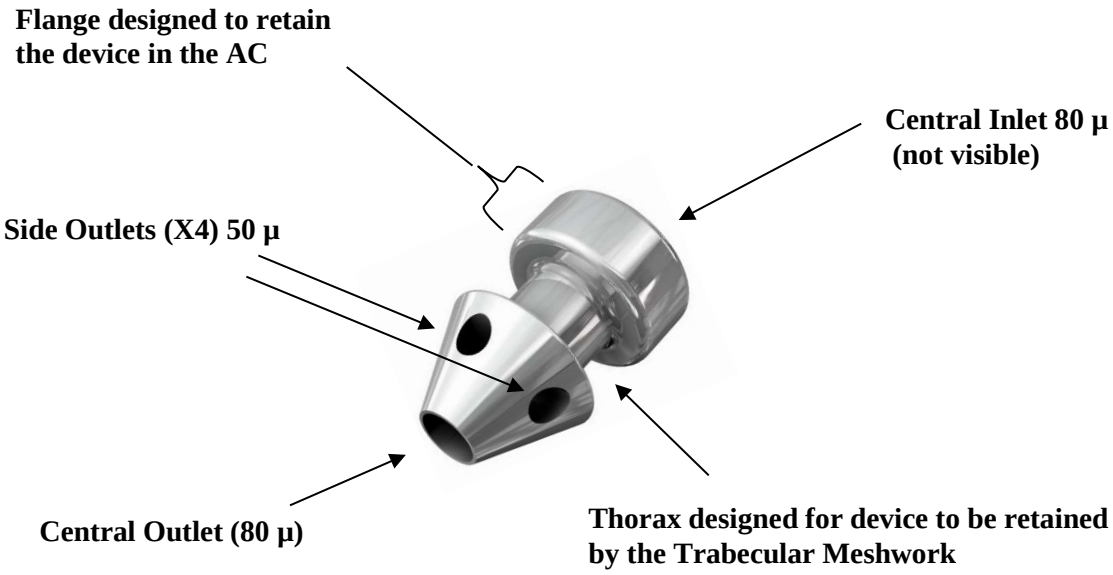

Figure 2. iStent *inject* **Stent (Model GTS400) Design**

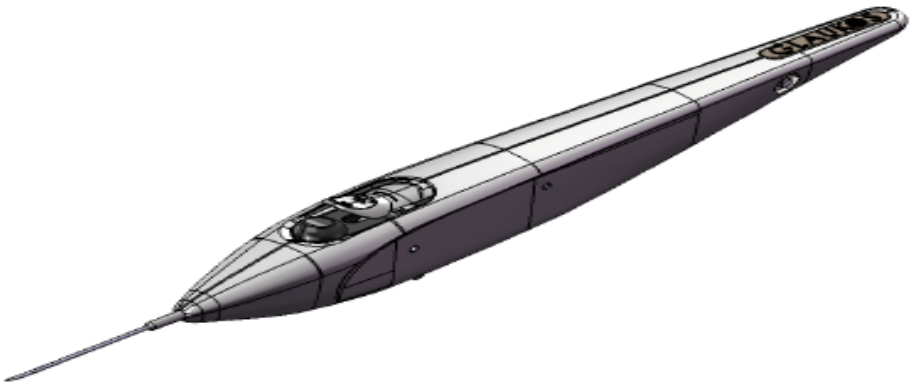

Figure 3. G2-M-IS Injector

When properly implanted, the iStent *inject* stent is intended to create a bypass through the trabecular meshwork into Schlemm's canal to improve aqueous outflow through the natural physiologic pathway. The implant is provided in a pre-loaded configuration allowing for precise implantation into Schlemm's canal. The injector has been designed by Glaukos Corporation to hold two stents to be implanted one at a time into Schlemm's canal.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of mild to moderate primary open angle glaucoma (POAG). These alternatives include:

- Other micro-invasive glaucoma surgery (minimally invasive glaucoma surgery [MIGS]) technologies
- Non-surgical treatment such as ocular hypotensive medications (topical eye drops or systemic ocular hypotensive medications)
- Laser treatment
- Other incisional glaucoma surgery

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The iStent *inject* has been marketed in European Union countries, Armenia, Australia, Brazil, Canada, Hong Kong, Singapore, and South Africa. The device has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may be reasonably associated with the use of the device include but are not limited to the following: anterior chamber shallowing, severe, prolonged, or persistent intraocular inflammation, aqueous misdirection, choroidal effusion, choroidal hemorrhage, corneal decompensation, corneal injury, corneal opacification, cyclodialysis cleft, damage to trabecular meshwork, hyphema, hypopyon, hypotony, hypotony maculopathy, IOL dislocation, iridodialysis, loss of vitreous, perforation of sclera, posterior capsular bag rupture, proliferative vitreoretinopathy, pupillary block, pupillary membrane formation, retinal detachment, retinal dialysis, retinal flap tears, secondary surgical intervention, including but not limited to glaucoma surgery, premature stent release, stent dislocation, stent not retrievable, stent not visible with gonioscopy, over implanted stents that are not visible with gonioscopy, stent malfunction, and vitreous hemorrhage.

For the specific adverse events that occurred in the pivotal clinical study, please see Tables 10-12 Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

1. Biocompatibility Testing

The biocompatibility testing outlined in the tables below was performed on the stent (or representative samples of the finished device) and the patient-contacting portion of the injector in accordance with the relevant parts of International Organization for Standardization (ISO) standard 10993.

Table 1a. Biocompatibility Testing - Stent

Test	Purpose	Acceptance Criteria	Results
Cytotoxicity:			
ISO Inhibition of Cell Growth	To determine the potential biological reactivity of a mammalian cell culture (L929) in response to the test article extract	Cell growth inhibition < 30%	Pass
ISO L929 MEM Elution Test	To determine the biological reactivity of a mammalian cell culture (L929) in response to the test article extract	No cell lysis or toxicity	Pass
Agar Diffusion Test	To determine the biological reactivity of a mammalian monolayer cell culture (L929) in response to the test article	No cell lysis or toxicity	Pass
Genotoxicity:			
Bacterial Reverse Mutation Study	To evaluate the potential of the test article to induce reverse mutations in histidine and tryptophan genes in *S. typhimurium* and *E. coli* respectively	No mutagenic changes	Pass
Mouse Bone Marrow Micronucleus Study	To determine the ability of the test article and/or its metabolites to induce micronuclei in maturing erythrocytes of mice	No toxicity or mutagenic effects	Pass
In Vitro Chromosomal Aberration Study	To determine the ability of the test article to induce chromosome aberrations, structural or numerical, in CHO cells in the presence or absence of an exogenous mammalian activation system	No chromosomal aberrations induced	Pass
Other:			
Intraocular Irritation Study in the Rabbit	To evaluate the potential of the test article extract to cause intraocular irritation or toxicity following an intracameral injection in rabbits	No evidence of irritation	Pass

Guinea Pig Kligman Maximization Test	To evaluate the allergenic potential or sensitizing capacity of the test article	No evidence of delayed dermal contact sensitization	Pass
Muscle Implantation in the Rabbit (2, 4, and 13 Weeks)	To evaluate the test article for local tissue responses and the potential to induce local toxic effects after implantation	No significant reaction	Pass
Acute Systemic Toxicity in the Mouse	To evaluate the test article extracts for potential toxic effects following a single-dose systemic injection in mice	No evidence of systemic toxicity	Pass
USP Material-Mediated Rabbit Pyrogen Study	To determine the potential presence of chemical pyrogens in extracts of the test article	Non-pyrogenic	Pass

Table 1b. Biocompatibility Testing - Injector

Test	**Purpose**	**Acceptance Criteria**	**Results**
Cytotoxicity:			
ISO Inhibition of Cell Growth	To determine the potential biological reactivity of a mammalian cell culture (L929) in response to the test article extract	Cell growth inhibition < 30%	Pass
ISO L929 MEM Elution Test	To determine the biological reactivity of a mammalian cell culture (L929) in response to the test article extract	No cell lysis or toxicity	Pass
Agar Diffusion Test	To determine the biological reactivity of a mammalian monolayer cell culture (L929) in response to the test article	No cell lysis or toxicity	Pass
Other:			
Intraocular Irritation Study in the Rabbit	To evaluate the potential of the test article extract to cause intraocular irritation or toxicity following an intracameral injection in rabbits	No evidence of irritation	Pass
Guinea Pig Kligman Maximization Test	To evaluate the allergenic potential or sensitizing capacity of the test article	No evidence of delayed dermal contact sensitization	Pass
Intracutaneous	To evaluate the test article for	Non-irritating	Pass

Injection Test	potential irritation effects as a result of an intracutaneous injection in New Zealand White rabbits		
Acute Systemic Toxicity in the Mouse	To evaluate the test article extracts for potential toxic effects following a single-dose systemic injection in mice	No evidence of systemic toxicity	Pass

2. Physico-chemical Testing

The purpose of the physico-chemical testing is to ensure that any toxic products that may result from processing, aging, and degradation do not affect the biocompatibility of the test results. The physico-chemical testing was leveraged from PMA P080030 (see page 6 of the SSED for P080030 https://www.accessdata.fda.gov/cdrh_docs/pdf8/P080030B.pdf.)

3. Physical and Mechanical Testing

The purpose of the physical and mechanical testing was to evaluate the iStent *inject* stent and injector in accordance with the requirements of ANSI Z80.27 and the FDA Guidance document for MIGS devices. These tests are summarized in Table 3 below:

Table 3. Physical and Mechanical Testing

Test	Acceptance Criteria	Results	Analysis Type
Surface & Edge Quality	Surface & edge defects not observed at ≥ 10x magnification or visible to a trained observer without magnification	Pass	Attribute data from etched and coated stents used for SEM analysis at 100X to 350X magnification
Dimensions	Stent length, width, thorax width, and lumen diameter are within tolerances	Pass	Variable data from stents tested as part of process validation
Physical Stability	Visual inspection, dimensional stability, and heparin coating are maintained following immersion in Solution (BSS) for 14 days at 35°C ± 2°C.	Pass	Variable and attribute data from etched & coated stents
Pressure/Flow Characteristics	Stent has negligible flow resistance	Pass	Numerical modeling, including computational fluid dynamics, was used to evaluate the flow through the stents over physiologically relevant boundary conditions.
Structural Integrity	Stent will maintain its structural integrity after implantation with the injector	Pass	Finite Element Analysis was performed

	velocity range seen clinically.		
Insertion Testing	Injector meets performance specifications, and no change in the physical properties of the stent	Pass	Variable and attribute data obtained as part of process validation: • 4 trigger actuations in 15 devices (60 total) tested for implantation velocity • 30 devices tested for singulation (2 stents per device = 60 samples) • 30 devices tested for trocar penetration • 60 stents implanted into corneal rim tissue, and visual/dimensional inspection performed on stents
Surface Coating Evaluation	Heparin coating present and functional through 3 years, as determined by Eosin dye staining and wettability testing	Pass	Variable and attribute data from titanium coupons that represent the finished coated stent
Corrosion Resistance	Corrosion resistance testing was performed in accordance with ASTM F2129 (no specific acceptance criteria per this standard)	The test lab concluded that the biomedical devices displayed acceptable corrosion resistance to pitting and crevice corrosion	Attribute data from titanium coupons that represent the coated stent

4. Sterilization, Package Integrity, Shelf Life, and Transport Stability

The iStent *inject* is sterilized by gamma radiation (25-40 kGy cycle). A sterilization validation for the device was performed in accordance with ISO 11137-1:2006 to validate the irradiation dose and to confirm that a sterility assurance level (SAL) of 10^{-6} is achieved. The sterilization dose was established in accordance with ISO 11137-2:2013. Additional dose audits are performed at

least once per every 3 months during which there is production, in order to reaffirm the sterilization dose of 25kGy and assess any fluctuations in bioburden. Documented evidence is provided in the validation final report to demonstrate that the sterilization process delivers a minimum Sterility Assurance Level (SAL) of 10^{-6}. In addition, the test method for bacterial endotoxin testing was validated. Endotoxin levels on the intraocular stents were below the FDA recommended limit of ≤0.2 EU/device.

Accelerated shelf-life studies were performed for the final packaging configuration to allow extrapolation of testing intervals under accelerated conditions to intervals at normal storage conditions. The corresponding real-time shelf life was calculated by multiplying the studied time period by $2.0^{(Ta-To)/10}$ where T_a is the accelerated temperature (45° C) and T_o is the ambient storage temperature (23° C). Real time shelf-life studies to confirm the accelerated shelf-life study results are currently in progress.

Product stability testing was performed for the stent and the injector, and package integrity testing was performed for the sterile barrier.
For product stability, the following tests were performed:

- Visual Inspection: Protective Tube Retained
- Visual Inspection: External Plastic Part Durability
- Visual Inspection: Stent Retention
- Dimensional Inspection: Trocar Extension Length
- Functional Test: Trigger Lockout
- Functional Test: Insertion Sleeve Retraction Force
- Functional Test: Stent Implantation
- Velocity and Singulation
- Trigger Force Testing
- Dimensional Inspection: Collet Extension Distance
- Functional Test: Insertion Sleeve Pull Test
- Function Test: Tissue Implantation
- Function Test: Trocar Penetration

For package integrity, the following tests were performed:

- ISTA P2A Transportation test/simulation and environmental conditioning per ASTM D4169
- Seal strength peel testing and bubble leak test per ASTM F88 and ASTM F 2096, respectively

Package integrity and stability data support a shelf-life of 3 months from the date of sterilization.

Table 4. Sterility, Shelf Life, and Transport Stability Testing

Test	Purpose	Acceptance Criteria	Results

Gamma Sterilization Validation	Evaluate sterility	Sterility assurance level of 10^{-6}	Pass
Bacterial Endotoxin	Evaluate endotoxin levels on implant	$\leq$ 0.2 EU/device	Pass
Product Stability	Evaluate product stability for the shelf life period	Injector and stent meet all visual, dimensional and performance requirements	Pass
Package Integrity	Evaluate seal integrity for the shelf life period	Seal strength peel testing $\geq$ 1.0 lbf, and no failures for bubble leak test	Pass

4. iStent *inject* injector Testing to Demonstrate Equivalency

The iStent *inject* implants were implanted using an injector that is slightly different from the commercially available injector. Minor changes were made to some of the IDE injector handpiece to improve manufacturability and to accommodate production scale-up. A summary of the changes and the testing that was performed to demonstrate equivalency in safety and performance is presented below in Table 5. Clinical testing is not available for the modified injector.

Table 5. Summary of Key Differences Between the iStent inject IDE and Commercial Injector and Testing to Demonstrate Equivalency

Description of Minor Changes	Affected Components	Testing Performed
Material Changes	• Trigger Spring from 302 SS to 17-PH SS • CP Retraction Button from LCP to Nylon w/ teal colorant • Collet material changed from Nitinol Alloy to 304 SS	• Biocompatibility Testing • Shelf Life: Product Stability • Process Validation (Performance) • Sterilization Validation • Human Factors Testing

Table 5. Summary of Key Differences Between the iStent inject IDE and Commercial Injector and Testing to Demonstrate Equivalency		
Description of Minor Changes	**Affected Components**	**Testing Performed**
Injector Design and Process Changes	• Insertion Sleeve - sharp to blunt • Insertion Assembly – single component w/ elimination of bushing and seal and slightly longer insertion tube • Left & Right Housings – Slightly larger, cosmetic changes. • Collet Holder Assembly - overmolded, • Trocar Assembly – crimped • Trigger Button – metal pin now molded into plastic	• Biocompatibility Testing of the assembled device • Shelf Life Studies: Product Stability • Process Validation (Performance) • Sterilization Validation • Human Factors Testing
Components now cleaned at vendor	• Hammer Cam • CP link • CP Retraction Button • Trigger Button • Collet Holder Assembly • Trocar Assembly • Left and Right Housings • Tray Packaging	All Cleaning Processes (at Glaukos or at vendor) were validated, i.e. • Plastic Parts • Metal Parts • Insertion Sleeve Etching & Cleaning • Insertion Tube • Small Plastic Parts

5. Magnetic Resonance Imaging (MRI) Safety Information

Non-clinical testing has demonstrated that the iStent *inject* is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 3T or less
- Maximum spatial gradient magnetic field of 4,000 gauss/cm (40 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4W/kg

Under the scan conditions defined above, the iStent *inject* is not expected to produce a clinically significant temperature rise after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends less than 15 mm from the device when imaged with a gradient echo pulse sequence and a 3.0 T MRI system.

X. SUMMARY OF PIVOTAL CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the iStent *inject* for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG) in the US under IDE #G100326. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

504 patients (505 eyes) were treated from January, 2012 through August, 2015 (one patient had both eyes enrolled in the study and it was reported as a protocol violation). The database for this PMA reflected data through November 13, 2017 and included 505 eyes randomized at 40 investigational sites.

The study was a prospective, randomized, comparative, multicenter investigation conducted in the United States, in which a total of 505 eyes from 40 sites were randomized in a 3:1 fashion to undergo either implantation of the iStent *inject* Trabecular Micro-Bypass System Model G2-M-IS after uncomplicated cataract surgery (iStent *inject* group) or to undergo cataract surgery without implantation of the iStent *inject* (Control group). A total of 387 eyes were randomized to the iStent *inject* group and 118 eyes were randomized to the Control group. The study was initiated in September 2011 under IDE G100326. At the time of the database lock for this report, all available eyes had reached the time point at which the safety and effectiveness endpoints are evaluated, i.e., 24 months postoperative. The database for this PMA was locked on November 13, 2017.

The subjects and Medical Monitor were masked to treatment assignments. Each IOP measurement was to be performed using Goldmann applanation by two observers, one of whom was masked to the treatment group assignment.

There were two (2) hypotheses for the primary effectiveness endpoint defined as $\geq$ 20% reduction in medication-free diurnal IOP at Month 24. The first hypothesis was that a larger proportion of eyes who received the iStent *inject* would meet the primary effectiveness endpoint than those who received cataract surgery alone. The second hypothesis was that the 24-month IOP response rate of the iStent

inject group would be better than 50%. This hypothesis was to be tested if the observed Cataract surgery-only response rate was greater than 35%.

The sample size calculation was based on the hypothesis testing for effectiveness, and evaluation for safety. For effectiveness, the sample size was estimated to be at least 376 eyes (282 iStent *inject* group and 94 control) for the first set of hypotheses, and 274 iStent *inject group* eyes for the second set of hypotheses. For safety, a sample size of 300 iStent *inject group* eyes at 24 months is sufficient to detect safety events occurring at a rate of 1% or greater. With allowance for up to 10% losses per year to follow-up at two years, at least 370 iStent *inject group* eyes and 123 control eyes were to be randomized. Therefore, the sample size was set at 500 randomized eyes (375 iStent *inject* group and 125 control).

The study included a medical monitor, data safety monitoring board (DSMB), and specular microscopy reading center.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the iStent *inject* Pivotal Trial was limited to patients who met the following key preoperative inclusion criteria:

   - Male or female, 45 years of age or older
   - Diagnosis of mild to moderate primary open-angle glaucoma in the designated study eye
   - At the Screening visit, a medicated mean (or median) IOP ≤ 24 mmHg on a regimen of 1 – 3 medications
   - At the Baseline visit, following medication washout, an unmedicated mean diurnal IOP > 21 mmHg and ≤ 36 mmHg, which also had to be ≥ 3.0 mmHg higher than the medicated IOP measured at the Screening Visit, in the study eye.
   - Gonioscopy confirming normal open angle in the designated study eye as defined by Shaffer grade ≥ 3, and absence of peripheral anterior synechia (PAS), rubeosis or other angle abnormalities that could impair proper placement of stent
   - Clinically significant age-related cataract eligible for phacoemulsification and BCVA 20/40 or worse with medium Brightness Acuity Meter (BAT)
   - Ability to provide an adequate, interpretable visual field
   - Corneal endothelial cell criteria based on images taken prior to Operative visit as follows:
     - minimum endothelial cell density as shown in Table 5 below
     - maximum coefficient of variation (CV) = 0.45

Table 6. Minimum Endothelial Cell Density at Screening

Age at time of enrollment	Minimum endothelial cell density
45 years	2200 cells/mm^2
46 to 55 years	2000 cells/mm^2
56 to 65 years	1800 cells/mm^2
> 65 years	1600 cells/mm^2

- Patients able and willing to provide written informed consent and to attend scheduled follow-up exams for two years postoperatively (and up to five years postoperatively as part of a post-approval study)

Enrollment in the iStent *inject* Pivotal Trial was limited to subjects who did not undergo complications of cataract surgery such as posterior capsular rupture, vitreous loss or complications associated with posterior chamber IOL implantation.

Patients were not permitted to enroll in the study if they met any of the following key exclusion criteria related to glaucoma or IOP:

- pigmentary or pseudoexfoliative glaucoma
- traumatic, uveitic, neovascular, or angle-closure glaucoma; or glaucoma associated with vascular disorders
- functionally significant visual field loss
- prior incisional glaucoma surgery
- prior selective laser trabeculoplasty (SLT) within 90 days prior to screening
- prior argon laser trabeculoplasty (ALT)
- prior iridectomy or laser iridotomy
- visual field (mean deviation) worse than -12 db
- ineligible for ocular hypotensive medication washout period as determined by the investigator: a) visual field status would be placed at risk by washout period or b) unmedicated IOP after washout would be expected to exceed 36 mmHg
- clinically significant corneal dystrophy, active inflammation or surgery that may interfere with IOP measurement reliability
- elevated episcleral venous pressure such as associated with active thyroid orbitopathy or cavernous sinus fistula
- use of systemic medications that could cause an increase in IOP

2. Follow-up Schedule
   All patients were scheduled to return for follow-up examinations 6 hrs, Day 1, Week 1, Month 1, Month 3, Month 6, Month 11, Month 12, Month 23, and Month 24.

Preoperatively, the evaluations that were performed in relation to the index procedure are listed below in Table 7. Postoperatively, the objective parameters measured during the study include those assessments listed below in Table 7.

The key timepoints are shown below in **Table 7** and in the tables summarizing safety and effectiveness below.

Table 7. Schedule of Events and Procedures

Procedure	**Screening**	**Baseline**	**Operative**	**6 Hr**	**Day 1**	**Week 1**	**Month 1**	**Month 3**	**Month 6**	**Month 11[1]**	**Month 12**	**Month 18**	**Month 23[1]**	**Month 24**
Informed Consent	X													
Ocular Medical History	X	X												
Ocular Medication Assessment	X	X			X	X	X	X	X	X	X	X	X	X
Medical History/ Demographics	X	X												
Medication Assessment	X	X			X	X	X	X	X	X	X	X	X	X
Manifest Refraction	X	X					X	X	X	X	X	X	X	X
Best Corrected VA (Snellen) with BAT	X													
Best Spectacle Corrected VA (ETDRS)		X					X	X	X	X	X	X	X	X
Pinhole VA					X	X								
Slit Lamp Exam	X				X	X	X	X	X	X	X	X	X	X
Specular Microscopy	X							X	X		X	X		X
IOP via Applanation Tonometry	X			X	X	X	X	X		X		X	X	
Diurnal IOP via Applanation Tonometry		X							X		X			X
Gonioscopy (all subjects)	X				X[2]	X[2]	X	X	X	X	X	X	X	X
Ultrasound Biomicroscopic (UBM) Imaging							X[3]	X[3]	X[3]		X[3]	X[3]		X[3]
Dilated Fundus Exam	X						X	X	X		X	X		X
Clinical Assessment of Nerve Abnormality	X						X	X	X		X	X		X
Optic Nerve Head Imaging[4]	X								X		X	X		X
Vertical C/D Ratio	X								X		X	X		X
Visual Field	X								X		X	X		X
Pachymetry	X								X		X	X		X
Randomization			X											
Surgical Data			X											
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X
Subjective Assessment		X			X	X	X	X	X	X	X	X	X	X
VFQ-25 Questionnaire		X					X		X		X			X
OSDI Questionnaire		X					X		X		X			X
PHQ-9 Questionnaire		X					X		X		X			X

1. One-month washout visit – subjects on ocular hypotensive medication(s) at Month 11 visit or at Month 23 visit were washed out of medications in study eye for one month.
2. Gonioscopy was performed unless other changes (e.g., corneal edema) made it too difficult to do so.
3. UBM was performed if stent visualization was not possible with gonioscopy or if elevated IOP > 30 mmHg at one month or l later.
4. Optic nerve head imaging was performed at screening and Months 6, 12, 18, and 24 unless certain conditions (e.g., small pupil, dry eye) made it too difficult to do so.

3. <u>Clinical Endpoints</u>

With regard to safety, anticipated and unanticipated AEs were reported for all subjects randomized in the study per the treatment that they actually received. Best Corrected Visual Acuity (BCVA), central corneal pachymetry, slit lamp

and fundus exams, gonioscopy and central corneal endothelial cell density (ECD) were also used to assess safety.

With regard to effectiveness, the primary effectiveness endpoint was the proportion of eyes with ≥ 20% decrease in the 24-month medication-free mean diurnal intraocular pressure (DIOP) from baseline.

Subjects were defined as non-responders if they did not achieve the primary effectiveness endpoint, they were missing the 24-month IOP assessment outcomes, if ocular hypotensive medications were not washed out at the 24-month visit, if they underwent an IOP-affecting secondary surgical procedure (e.g., laser trabeculoplasty, trabeculectomy, shunt or valve placement) prior to the 24-month visit, experienced hypotony (IOP < 6 mmHg) associated with clinically significant findings, experienced no light perception, or if they underwent a procedure to reposition or remove an iStent *inject.*

The secondary effectiveness endpoint was diurnal IOP reduction from baseline at Month 24. The diurnal IOP at 24 months for the subjects that did not meet criteria comparable to those listed above for the primary endpoint was imputed by the baseline IOP.

With regard to success/failure criteria, each endpoint required a comparison between the iStent *inject* and Control groups. The primary effectiveness analysis was performed using the Effectiveness Cohort, comprised of subjects randomized to the iStent *inject* group who received 2 stents and subjects randomized to the control group.

B. <u>Accountability of PMA Cohort</u>

At the time of database lock, of 868 eyes enrolled in the PMA study, 54.7% (475/868) are available for analysis at the 24-month postoperative visit.

Of the 868 eyes enrolled, 41.2% (n/N = 358/868) were discontinued prior to surgery, primarily due to failure to meet eligibility criteria or withdrawal of consent prior to the operative day. An additional 5 eyes (0.6%; 5/868) were discontinued due to cataract surgery-related complications rendering them ineligible for study randomization. The remaining 58.2% (n/N = 505/868) eyes were randomized. Upon completion of uncomplicated cataract surgery, 387 eyes were randomized to the iStent *inject* group, and 118 eyes were randomized to the Control group, in which no additional surgery was planned. At 24 months postoperatively, 367 eyes in the iStent *inject* group and 108 Control group eyes completed the study.

The outcomes provided were analyzed according to three (3) separate population cohorts:

- The Intent to Treat (ITT) population was defined as all randomized eyes. Eyes were grouped according to their randomization assignment (as randomized).
- The Effectiveness Cohort was used for the effectiveness analyses. The Effectiveness Cohort included 380 eyes randomized to the iStent *inject* group who were implanted with 2 stents and 118 subjects randomized to the control group.
- The Safety population was defined as all randomized eyes. All subjects in the Safety population were analyzed according to the treatment they actually received (i.e., 386 subjects who received iStent *inject* in conjunction with cataract surgery and 119 eyes that underwent cataract surgery only).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a MIGS (minimally invasive glaucoma surgery) study performed in the US. The demographics and preoperative characteristics of the study population were as follows:

Table 8. Demographics
ITT Population

Parameter		Cataract Surgery with iStent *inject* N = 387	Cataract Surgery Only N = 118	Total N = 505
Age (Years)	Mean	69.0	70.1	69.2
	Standard Deviation	8.2	7.7	8.1
	Median	69	71	70
	Minimum	45	46	45
	Maximum	98	86	98
	P-value[1]	0.164		
	< 60	46/387 (11.9%)	12/118 (10.2%)	58/505 (11.5%)
	60 to < 70	151/387 (39.0%)	42/118 (35.6%)	193/505 (38.2%)
	70 to < 80	156/387 (40.3%)	52/118 (44.1%)	208/505 (41.2%)
	≥ 80	34/387 (8.8%)	12/118 (10.2%)	46/505 (9.1%)
	P-value[2]	0.798		
Gender	Male	162/387 (41.9%)	54/118 (45.8%)	216/505 (42.8%)
	Female	225/387 (58.1%)	64/118 (54.2%)	289/505 (57.2%)
	P-value[2]	0.459		
Race/ Ethnicity	White	282/387 (72.9%)	86/118 (72.9%)	368/505 (72.9%)
	Hispanic/Latino	24/387 (6.2%)	10/118 (8.5%)	34/505 (6.7%)
	Black	77/387 (19.9%)	19/118 (16.1%)	96/505 (19.0%)
	Asian	3/387 (0.8%)	1/118 (0.8%)	4/505 (0.8%)
	Other			
	American Indian	1/387 (0.3%)	0/118 (0.0%)	1/505 (0.2%)
	East Indian	0/387 (0.0%)	1/118 (0.8%)	1/505 (0.2%)
	Portuguese	0/387 (0.0%)	1/118 (0.8%)	1/505 (0.2%)
	P-value[2]	0.221		

Study Eye	OD	205/387 (53.0%)	64/118 (54.2%)	269/505 (53.3%)
	OS	182/387 (47.0%)	54/118 (45.8%)	236/505 (46.7%)
	P-value[2]	0.834		
POAG	Yes	387/387 (100.0%)	118/118 (100.0%)	505/505 (100.0%)

[1] Two-sample t-test
[2] Fisher's exact test

Table 9. Preoperative Characteristics
ITT Population

Parameter		Cataract Surgery with iStent *inject* N = 387	Cataract Surgery Only N = 118	Total N = 505
Number of Ocular Hypotensive Medications at Screening	1	224/387 (57.9%)	71/118 (60.2%)	295/505 (58.4%)
	2	98/387 (25.3%)	30/118 (25.4%)	128/505 (25.3%)
	3	63/387 (16.3%)	17/118 (14.4%)	80/505 (15.8%)
	4	2/387 (0.5%)	0/118 (0.0%)	2/505 (0.4%)
	P-value[2]	0.943		
Visual Field Mean Deviation (MD) at Screening (dB)	Mean	-3.392	-3.357	-3.384
	Standard Deviation	3.285	3.143	3.249
	Median	-2.79	-3.07	-2.89
	Minimum	-12.58	-11.67	-12.58
	Maximum	3.12	2.04	3.12
	P-value[1]	0.915		
Corneal Thickness at Screening (μm)	Mean	546.49	546.06	546.39
	Standard Deviation	36.16	35.74	36.03
	Median	545.0	548.5	546.0
	Minimum	455.0	448.0	448.0
	Maximum	620.0	620.0	620.0
	P-value[1]	0.909		
Medicated IOP at Screening (mmHg)	Mean	17.54	17.54	17.54
	Standard Deviation	2.99	2.78	2.94
	Median	17.5	18.0	17.5
	Minimum	9.0	11.0	9.0
	Maximum	26.0	24.0	26.0
	P-value[1]	0.997		
Unmedicated IOP at Baseline (mmHg)	Mean	24.83	24.50	24.75
	Standard Deviation	3.34	3.08	3.28
	Median	24.0	23.4	23.8
	Minimum	20.8	20.7	20.7
	Maximum	35.8	34.3	35.8
	P-value[1]	0.328		
BSCVA at Baseline LogMAR	Mean (Snellen)	0.234 (20/34)	0.232 (20/34)	0.234 (20/34)
	Standard Deviation	0.168	0.161	0.166
	Median (Snellen)	0.22 (20/33)	0.20 (20/32)	0.22 (20/33)
	Minimum (Snellen)	-0.10 (20/16)	-0.08 (20/17)	-0.10 (20/16)
	Maximum (Snellen)	1.00 (20/200)	1.00 (20/200)	1.00 (20/200)
	P-value[1]	0.901		
Shaffer Angle Grade at Screening	III (25 - 35)	142/387 (36.7%)	40/118 (33.9%)	182/505 (36.0%)
	IV (> 35)	245/387 (63.3%)	78/118 (66.1%)	323/505 (64.0%)
	P-value[2]	0.661		

Oral medications count as 1 medication. Combination medications count as 2 medications. Two subjects in the Cataract surgery with iStent *inject* group took Diamox at Screening.
[1] Two-sample t-test
[2] Fisher's exact test

Operative parameters are provided for the iStent *inject* portion of the procedure (**Table 10**). In one of the 387 eyes, after successful cataract extraction and IOL implantation, and subsequent randomization to the iStent *inject* group, stent implantation was not attempted as a result of excessive coughing (i.e., 0 stents implanted). Of the 387eyes that were implanted with stents, 380 eyes (98.2%; 380/387) were implanted with 2 stents. Four eyes (1.0%; 4/387) were implanted with 3 stents and 2 eyes (<1%) were implanted with 1 stent.

In most eyes (85.5%; n/N = 331/387, only a single injector was employed. No associated clinical sequelae were noted in any cases in which a second injector was used. No difficulties with implantation were reported in the majority of cases (81.4%; n/N = 315/387). No associated clinical sequelae were noted in any cases in which stent implantation difficulty was reported.

Table 10. Operative Parameters — iStent *inject* Portion of Procedure ITT Population

	N = 387 Subjects	
	Number	**Percent**
# of Implants		
Yes	386	99.7%
1 Stent	2	0.5%
2 Stents	380	98.2%
3 Stents	4	1.0%
No	1	0.3%
# of Attempts		
1	263	68.0%
2	76	19.6%
3	29	7.5%
>3	18	4.7%
NA	1	0.3%
# of Injector Used[1]		
1	331	85.5%
2	55	14.2%
NA	1	0.3%
Difficulties with Implantation[1]		
Yes	71	18.3%
No	315	81.4%
NA	1	0.3%

Percent = Number ÷ N × 100%.

The iStent *inject* was not attempted for a subject due to coughing fit after randomization.

1. Reports of use of a second injector and of stent implantation difficulty are not mutually exclusive. Further, the same reason could be reported for 1 eye in both categories. The most common/notable reasons for use of a second injector include first injector did not deploy 2 stents (5.4%;

n = 21), stent not adequately seated in trabecular meshwork (TM) (5.2%; n = 20), poor visibility (1.3%; n = 5), stent dislodged during I/A (0.3%; n = 1). The most common/notable reasons for stent implantation difficulty include injector did not deploy stent (5.9%; n = 23), stent not adequately seated in TM (6.2%; n = 24), injector initially did not (but did eventually) deploy stent (2.1%; n = 8), poor visibility (1.6%; n = 6); 2 stents implanted in same location (0.3%; n = 1). In these reports of 2nd injector used and/or stent implantation difficulty, no associated clinical sequelae were noted in any cases.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety cohort of 505 eyes (386 iStent *inject* and 119 control), of which 475 (366 iStent *inject* group and 109 control) eyes were available for the 24-month evaluation. The key safety outcomes for this study are presented below in **Tables 11 to 13**.

Best Spectacle Corrected Visual Acuity (BSCVA)

Most eyes in both groups achieved best spectacle corrected visual acuity (BSCVA) of 20/40 or better at Month 24, with a slightly higher proportion of eyes achieving BSCVA of 20/40 or better in the iStent *inject* arm (98.9%; 361/365) than in the control group (98.2%; 107/109).

Adverse effects (AEs) that occurred in the PMA clinical study

Intraoperative AEs

A summary of intraoperative AEs is shown in **Table 11**. Because final study eligibility and randomization to treatment was determined post-cataract surgery, no subjects experiencing a predetermined cataract-surgery related AE such as posterior capsular rupture, vitreous loss or complications associated with posterior chamber IOL implantation were randomized. One eye experienced a corneal abrasion during cataract surgery and was subsequently randomized to the iStent *inject* group because this was not a clinically significant operative complication.

One of the 387 subjects randomized to iStent *inject* implantation experienced a coughing fit that resulted in increased positive pressure requiring a corneal suture. Therefore, no attempts to implant stents was made, and this subject was included in the control group of the Safety population. In the 386 iStent *inject* subjects implanted, 11 intraoperative AEs were reported during stent implantation (2.8%). Among these cases, there were 4 cases of 3 stents being implanted (1.0%) and two cases of only 1 stent being implanted (0.5%).

Table 11. Intraoperative Ocular Adverse Events in the Study Eye Safety Population

Intraoperative Events	Cataract Surgery with iStent *inject* N = 386 n (%)	Cataract Surgery Only N = 119 n (%)	Difference in % 95% CI[1]
Intraoperative adverse events during cataract surgery	**1 Reports from 1 subjects 0.3%**	**0 Reports from 0 subjects 0.0%**	**0.3% (-0.2%, 0.8%)**
Prolonged anterior chamber collapse	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Significant hyphema (i.e. ≥ 10% of anterior chamber)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Vitreous loss	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Vitrectomy	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Any choroidal hemorrhage	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Any choroidal effusion	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Significant iris damage	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Significant corneal injury	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Posterior capsular bag rupture	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Significant damage to trabecular meshwork	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Capsulorhexis tear	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Zonular rupture	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Evident zonular weakness or dehiscence	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Detached Descemet's membrane	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Incomplete phacoemulsification	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Complications associated with posterior chamber IOL implantation	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Anterior chamber IOL implantation	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Other			
Corneal abrasion	1 (0.3%)	0 (0.0%)	0.3% (-0.2%, 0.8%)
Intraoperative adverse events during iStent *inject* implantation	**11 Reports from 11 subjects 2.8%**	**NA**	**NA**
Any choroidal hemorrhage	0 (0.0%)		
Any choroidal effusion	0 (0.0%)		
Prolonged anterior chamber collapse	0 (0.0%)		
Significant hyphema (i.e. ≥ 10% of anterior chamber)	0 (0.0%)		
Significant iris damage	0 (0.0%)		
Significant corneal injury	0 (0.0%)		
Other			
1 stent implanted	2 (0.5%)		
2 stents implanted in same location	1 (0.3%)		
3 stents implanted	4 (1.0%)		
Corneal abrasion	3 (0.8%)		
Stent implanted in ciliary body	1 (0.3%)		

The counts (n) are the number of subjects reported with the corresponding events. % = n ÷ N × 100%.
There were no cases in which stent implantation was attempted and 0 stents were implanted (i.e., failure to implant 2 stents).

Postoperative AEs

There were no unanticipated adverse events. There were no reports of flat AC with lens cornea touch, shallow AC with iridocorneal apposition, shallow AC with peripheral iridocorneal apposition, wound dehiscence, endophthalmitis, corneal decompensation, choroidal hemorrhage or effusion, aqueous misdirection, cyclodialysis, hypotony at one month postoperative or later, hypotony maculopathy, atrophy/phthisis, cup-to-disc (CD) ratio increase of ≥ 0.3, loss of light perception or stent dislocation. Moreover, no cases of pupillary block or hypopyon were reported during the study.

A lower proportion of subjects in the iStent *inject* group experienced postoperative ocular AEs than in the Control group (54.1% of subjects [n/N = 209/386] in the iStent *inject* group and 62.2% of subjects [n/N = 74/119] in the Control group).

A list of the more common AEs (occurring at a rate of 2% or greater) and the associated rates are provided in **Table 12**. Anterior segment inflammation, which was generally mild, was reported in 5.7% (n/N = 22/386) of iStent *inject* group subjects and 4.2% (n/N = 5/119) of Control subjects.

Table 12. Postoperative Ocular Adverse Events Occurring at 2% or Greater in the Study Eye
Safety Population

Postoperative Events	Cataract Surgery with iStent *inject* N = 386 n (%)	Cataract Surgery Only N = 119 n (%)	Difference in % 95% CI[1]
Ocular surface disease	62 (16.1%)	20 (16.8%)	-0.7% (-8.6%, 7.1%)
Stent obstruction, partial or complete, regardless of how long the obstruction is present[1]	24 (6.2%)	NA	
Any intraocular inflammation (non pre-existing) remaining or arising after the protocol's specified medication regimen is complete[2]	22 (5.7%)	5 (4.2%)	1.5% (-2.8%, 5.8%)
Secondary surgical intervention[3]	21 (5.4%)	6 (5.0%)	0.4% (-4.2%, 5.0%)
Ocular allergies	11 (2.8%)	4 (3.4%)	-0.5% (-4.2%, 3.1%)
Loss of BSCVA of 2 line or more (10 letters or more on ETDRS chart) at or after 3 months postoperative	10 (2.6%)	5 (4.2%)	-1.6% (-5.6%, 2.3%)
Posterior vitreous detachment	10 (2.6%)	5 (4.2%)	-1.6% (-5.6%, 2.3%)
Foreign body sensation	9 (2.3%)	0 (0.0%)	2.3% (0.8%, 3.8%)
Blurred vision/visual disturbance	9 (2.3%)	2 (1.7%)	0.7% (-2.1%, 3.4%)
Extraocular inflammation	9 (2.3%)	2 (1.7%)	0.7% (-2.1%, 3.4%)
Epiretinal membrane	9 (2.3%)	3 (2.5%)	-0.2% (-3.4%, 3.0%)
IOP increase ≥ 10 mmHg vs. baseline IOP occurring at ≥ Month 1[4]	8 (2.1%)	1 (0.8%)	1.2% (-0.9%, 3.4%)
Perioperative ocular pain within 14 days of surgery	8 (2.1%)	1 (0.8%)	1.2% (-0.9%, 3.4%)
Vitreous floaters	8 (2.1%)	3 (2.5%)	-0.4% (-3.6%, 2.7%)
Corneal abrasion	8 (2.1%)	4 (3.4%)	-1.3% (-4.8%, 2.3%)
Corneal opacity	4 (1.0%)	3 (2.5%)	-1.5% (-4.5%, 1.5%)
Hyperemia	3 (0.8%)	7 (5.9%)	-5.1% (-9.4%, -0.8%)
Non-proliferative diabetic retinopathy	2 (0.5%)	3 (2.5%)	-2.0% (-4.9%, 0.9%)
IOP increase requiring management with oral or intravenous medications or with surgical intervention at ≥ Month 1[4]	1 (0.3%)	3 (2.5%)	-2.3% (-5.1%, 0.6%)

The counts (n) are the number of subjects reported with the corresponding events. % = n ÷ N × 100%.
There were no cases of iridodialysis and no cases of significant hyphema (≥10% of anterior chamber).

1. In certain cases of stent obstruction, the investigators reported associated findings of transient hyphema (n=8), inferior pigment (n=14) and/or focal goniosynechiae (n=10). In 8 cases, investigators reported obstruction of both stents. Three cases of stent obstruction were treated with laser; obstruction resolved in all three cases. Seventeen cases were persistent at Month 24. Of these 17 cases, the primary effectiveness endpoint was met in 9 cases despite no treatment with laser.
2. Three subjects in the iStent *inject* group had chronic iritis defined as anterior cells or flare of grade 1+ or worse persisting for more than 3 months postoperatively that recurs less than three months after discontinuing the initial postoperative steroid regimen.
3. The events of "Glaucoma progression requiring secondary surgical intervention' (4 iStent *inject* and 1 Cataract) and "Medication intolerance requiring surgical intervention" (1 iStent *inject* and 0 Cataract) were included.
4. The events of IOP increase requiring management with oral or intravenous medications or with surgical intervention at ≥ Month 1 and IOP increase ≥ 10 mmHg vs. baseline IOP occurring at ≥ Month 1 were mutually exclusive. The events of IOP increase requiring surgical intervention occurring at ≥ Month 1 were also included in the reports of "Secondary Surgical Intervention".

In addition to the AEs reported in **Table 12**, events that occurred at a rate of < 2% in both groups included age-related macular degeneration, chalazion, conjunctivitis, corneal guttata, cystoid macular edema, diplopia, disc hemorrhage, ectropion, glaucoma progression requiring surgical intervention, lattice degeneration, nerve fiber layer loss, ocular irritation, optic nerve thinning/cupping, visual field loss ≥ 2.5 dB and vitreous hemorrhage. AEs that occurred at < 2% in the iStent *inject* group included one case (0.3%; n/N = 1/386) each of blepharospasm, branch retinal vein occlusion, corneal edema ≥ 30 days, corneal striae, eyelash loss, iris atrophy, iris strand, medication intolerance requiring surgical intervention, ptosis, residual cortex, retinal detachment, retinal tear, and worsening glaucoma; 2 cases (0.5%; n/N = 2/386) each of anterior basement membrane dystrophy, extraocular papilloma, ocular pain, punctal stenosis, retinal drusen, retinal hemorrhage and retinal pigment epithelial changes; 3 cases (0.8%; n/N = 3/386) each of peripapillary atrophy, retinal flap tears, retinal hole and notching; 4 cases (1.0%; n/N = 4/386) of deep stents[1] and transient mild ocular discomfort; 5 cases (1.3%; n/N = 5/386) of subconjunctival hemorrhage and 7 cases (1.8%) of goniosynechiae. AEs that occurred at < 2% in the control group included 1 case (0.8%; n/N = 1/119) each of anterior scleritis, central retinal artery occlusion, corneal ulcer, flashes, iris neovascularization and IOL dislocation; and 2 cases (1.7%; n/N = 2/119) of extraocular trauma.

The study investigators determined for each intraoperative and postoperative ocular AE reported whether an event was considered serious. The proportion of eyes with serious AEs (SAEs) was 0.8%; (n/N=3/386) in the iStent *inject* group and 2.5% (n/N=3/119) in the control group. iStent *inject* group SAEs comprised 1 case each of mild partial stent obstruction that did not require intervention, retinal tear requiring laser retinopexy, and glaucoma progression requiring ExPress shunt implantation. SAEs reported for the control group consisted of 1 case each of blurred vision/visual disturbance; epiretinal membrane requiring vitrectomy with membrane peel, and central retinal artery occlusion and neovascularization requiring pan-retinal photocoagulation.

A total of 56 AEs reported for 48 iStent *inject* eyes (12.4%; n/N = 48/386) were determined to be device related including all cases of stent obstruction, deep stents, 3 stents implanted, 1 stent implanted, 2 stents

[1] In each of the four eyes with "deep stents," there was a single stent per eye that was unable to be visualized by either gonioscopy or UBM at the last 3 visits, despite being visualized intraoperatively and/or at an earlier postoperative exam. Among these cases, there were no associated clinical sequelae or secondary surgeries to modify device positioning, none experienced an endothelial cell loss >30% at 24 months or posterior segment sequelae, and three of the four eyes met the primary effectiveness endpoint.

implanted in the same location, and stent implanted in the ciliary body, which accounted for 36 of the 56 device-related AEs. Other AEs determined to be device-related included 8 cases (2.1%; n/N = 8/386) of intraocular inflammation, 7 cases (1.8%; n/N = 7/386) of goniosynechiae, 3 cases (0.8%) of intraoperative corneal abrasion, and 1 case (0.3%) each of iris strand and ocular irritation.

Secondary Surgical Interventions

Secondary ocular surgeries during the course of the study, some of which were to achieve further IOP reduction, occurred in 5.4% of iStent *inject* group subjects (n/N = 21/386) and 5.0% (n/N = 6/119) of subjects in the control group. Secondary surgeries reported in both groups are shown in **Table 13**.

Table 13. Surgical Interventions in the Study Eye Safety Population

Secondary Surgical Intervention	Cataract Surgery with iStent *inject* N = 386 n (%)	Cataract Surgery Only N = 119 n (%)	Difference in % 95% CI[1]
Overall	**22 Reports from 21 subjects 5.4%**	**7 Reports from 6 subjects 5.0%**	**0.4% (-4.2%, 5.0%)**
IOL exchange[1]	1 (0.3%)	0 (0.0%)	0.3% (-0.2%, 0.8%)
IOL repositioning	0 (0.0%)	1 (0.8%)	-0.8% (-2.5%, 0.8%)
Laser for stent obstruction[2]	3 (0.8%)	NA	
Laser retinopexy	6 (1.6%)	0 (0.0%)	1.6% (0.3%, 2.8%)
Panretinal photocoagulation	0 (0.0%)	1 (0.8%)	-0.8% (-2.5%, 0.8%)
Posterior vitreolysis	2 (0.5%)	0 (0.0%)	0.5% (-0.2%, 1.2%)
Removal of residual cortex	1 (0.3%)	0 (0.0%)	0.3% (-0.2%, 0.8%)
Selective laser trabeculoplasty	2 (0.5%)	3 (2.5%)	-2.0% (-4.9%, 0.9%)
Trabeculectomy/Express Shunt	4 (1.0%)	1 (0.8%)	0.2% (-1.7%, 2.1%)
Vitrectomy[3]	1 (0.3%)	0 (0.0%)	0.3% (-0.2%, 0.8%)
Vitrectomy with membrane peel	1 (0.3%)	1 (0.8%)	-0.6% (-2.3%, 1.1%)

The counts (n) are the number of subjects reported with the corresponding events. % = n ÷ N × 100%.
All SSIs, regardless of reason, were included.
There were no cases of free-floating stents leading to sequelae in the posterior segment.

1. The reason for IOL exchange was dysphotopsia despite good spherical/astigmatic refractive outcome. The dysphotopsia resolved following exchange of the original spheric acrylic IOL with an aspheric silicone IOL of equivalent refractive power.
2. Stent obstruction was treated with argon laser iridoplasty in 2 cases and Nd:YAG laser membranectomy in 1 case.
3. The reason for vitrectomy was retinal detachment repair.

Other Postoperative Observations

Reporting of other ocular observations was at the study investigator's discretion. Similar data may not be reported for every patient, or consistently within the course of a given patient's study participation. Consequently, no conclusions regarding the overall frequency of these findings can be drawn from the incidence rates noted. In no cases were both stents not visible on the operative day. The other ocular

observations that were reported operatively included, but were not limited to: 1 implanted stent not visible on the operative day (3.6%; n/N = 14/386). In 12 of these 14 eyes, stents were visualized postoperatively. In the remaining 2 cases, non-visible stents were detected via ultrasound biomicroscopy (UBM) prior to Month 24 with minimal associated clinical sequelae besides "deep stent" as an adverse event (AE). The other ocular observations that were reported postoperatively included but were not limited to: goniosynechiae (7.7%; n/N = 30/386); microhyphema (3.9%; n/N = 15/386); and corneal endothelial pigment (0.8%; n = 3). Early IOP increase ≥ 10 mmHg (i.e. prior to Month 1) or IOP increase < 10 mmHg was reported in 2.6% (n/N = 10/386) eyes in the iStent *inject* group and 5.0% (n/N = 6/119) eyes in the Control group.

Corneal Endothelial Cell Density

There was little difference in endothelial cell loss (ECL) between the iStent *inject* and Control groups. Results were consistent with previous reports of cataract surgery-related ECL. The mean percent change in ECD from baseline to 24 months was -13.1% (SD 12.4; 95% CI -14.4%, -11.8%) for the iStent *inject* group and -12.3% (SD 12.7%; 95% CI -14.8%, -9.8%) for the control group.

A similar proportion of eyes in each group (10.4%; (40/386) in the iStent *inject* group and 9.5%; 11/119) in the control group) experienced ECL > 30% at 24 months postoperatively.

2. Effectiveness Results

The analysis of effectiveness was based on the 380 evaluable patients at the 24-month time point. Results from the primary and secondary endpoints are shown in **Table 14**. The primary effectiveness endpoint was met, with 75.8% (288/380) in the iStent *inject* group and 61.9% (73/118) in the Control group achieving a clinically significant (≥ 20%) reduction in medication-free diurnal IOP from baseline at 24 months. This difference between groups was statistically significant (p=0.003).

The secondary endpoint, a clinically significant mean change in medication-free diurnal IOP from baseline at 24-month postoperative examination, was met. The mean reduction in medication-free mean diurnal IOP from baseline to 24 months was 7.0 mmHg (SD 4.0) in the iStent *inject* group compared to 5.4 mmHg (SD 3.7) in the control group (p <0.001).

Table 14 Primary and Secondary Effectiveness Results

Effectiveness Endpoint (Evaluated at 24 Months Postoperatively)	Cataract Surgery with iStent *inject* N = 380	Cataract Surgery Only N = 118	Difference (iStent *inject* vs. control)	P-value for difference
Proportion of subjects with medication-free DIOP reduction ≥ 20% from baseline	75.8%	61.9%	13.9%	0.003[2]
Medication-free mean DIOP (mmHg) change from baseline[1]	-7.0	-5.4	-1.6	< 0.001[3]

Subjects without Month 24 medication-free diurnal IOP, or with IOP-related SSIs, loss of light perception or hypotony (IOP < 6 mmHg) associated with clinically significant findings prior to 24 months were treated as non-responders. iStent *inject* subjects with stent reposition or removal prior to 24 months were treated as non-responders.

1. The 24-month diurnal IOP values were subtracted from baseline diurnal IOP in all subjects, except for the non-responders described above. For the non-responders described above, the baseline diurnal IOP values were used for the 24-month diurnal IOP values (i.e., a change of 0 mmHg was used).
2. One-sided Fisher's exact test with a significance level of 0.025.
3. One-sided two-sample t-test with a significance level of 0.025.

Additional detail regarding the reasons patients did not achieve the primary endpoint (IOP non-responders) is shown in **Table 15**

Table 15. Non-Responder Categories at 24 Months
Effectiveness Cohort

	Cataract Surgery with iStent *inject* N = 380 n/N (%)	**Cataract Surgery Only N = 118 n/N (%)**
Total Non-Responders	92 (24.2%)	45 (38.1%)
Non-Responders: 24-month unmedicated diurnal IOP reduction from baseline < 20%	56 (14.7%)	26 (22.0%)
Non-Responders for reasons other than IOP reduction[1]	36 (9.5%)	19 (16.1%)
Secondary glaucoma surgery[2]	5 (1.3%)	3 (2.5%)
Other IOP-affecting secondary surgery[3]	0 (0.0%)	0 (0.0%)
Stent reposition or removal	0 (0.0%)	0 (0.0%)
Loss of light perception	0 (0.0%)	0 (0.0%)
Clinically significant hypotony	0 (0.0%)	0 (0.0%)
Did not complete medication washout – Safety concerns	12 (3.2%)	4 (3.4%)
Did not complete medication washout – Instructions not provided/followed[4]	0 (0.0%)	2 (1.7%)
Missing 24-month diurnal IOP data[4]	19 (5.0%)	10 (8.5%)
Death	4 (1.1%)	6 (5.1%)
Investigator's decision	1 (0.3%)	0 (0.0%)
Lost contact	8 (2.1%)	2 (1.7%)
Subject's decision	6 (1.6%)	2 (1.7%)

n = number of eyes with the corresponding responses. % = n ÷ N × 100%.
1 Subjects were included in the primary category of "Non-Responders for reasons other than IOP reduction".
2 Secondary glaucoma surgeries include trabeculectomy, and laser trabeculoplasty.
3 Other IOP-affecting secondary surgeries.
4 The outcomes of these subjects were imputed for the 24-month analysis.
There were 2 subjects on oral medication at 23 months and both subjects underwent washout. Hence, although any subjects on oral medication at 24 months would have been considered non-responders due to the potential to confound the endpoint analysis, there were no subjects in this category.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR Part 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 102 investigators of which none were full-time or part-time employees of the sponsor and 8 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 investigators
- Significant payment of other sorts: 8 investigators (one did not enroll subjects; site was closed prior to enrollment.)
- Proprietary interest in the product tested held by the investigator: 0 investigators
- Significant equity interest held by investigator in sponsor or covered study: 5 investigators (one did not enroll subjects; site was closed prior to enrollment.)

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. The iStent *inject* safety findings are further supported by the summary of commercial marketing experience. The iStent *inject* Trabecular Micro-Bypass System Model G2-M-IS has been marketed in European Union countries, Armenia, Australia, Brazil, Canada, Hong Kong, Singapore, and South Africa. Since commercial introduction in 2011, there have been 30,285 units distributed worldwide. There have been no product recalls, field safety notices, or product withdrawals since introduction of the iStent *inject* Trabecular Micro-Bypass System Model G2-M-IS. The significant body of postmarket experience outside the U.S. represents a highly favorable device safety profile and supports the safety results observed in the pivotal IDE trial.

B. For the pivotal trial of the iStent *inject*, the Ocular Surface Disease Index (OSDI©) was self-administered by study patients. The OSDI questionnaire contains 12 questions involving ocular symptoms, vision-related function and environmental triggers experienced by the patient during the past week, and is assessed on a scale of 0 to 100 with higher scores representing greater disability. **Table 17** summarizes the change in OSDI subscales and overall score from baseline. The mean improvements at 24 months from baseline were slightly higher in the iStent *inject* group compared to the control group involving ocular symptoms (-16.41 vs. -10.69) and vision-related function (-22.60 vs. -18.56) and similar involving environmental triggers (-7.41 vs. -7.70). The mean improvement in OSDI overall score at 24 months was also higher in the iStent *inject* group compared to the control group (-16.25 vs. -12.38). Further, the change involving each OSDI question from baseline at 2 years is shown in Table 17, and the results for each individual question of the

OSDI questionnaire at 2 years for the iStent *inject* group and control group is shown in Table 18. The questionnaire used to collect these data has not been validated, and therefore the true rates of these symptoms may differ from those presented in **Tables 16-18.**

Table 16
Change in OSDI Questionnaire Sub-Scale Score from Baseline
Safety Population

	Cataract Surgery with iStent *inject* Total Number of Subjects = 386				Cataract Surgery Only Total Number of Subjects = 119			
Statistics	**1M n (%)**	**6M n (%)**	**12M n (%)**	**24M n (%)**	**1M n (%)**	**6M n (%)**	**12M n (%)**	**24M n (%)**
Ocular Symptoms (Q1, Q2, Q3)								
N	382	376	367	361	117	118	115	109
Mean	-11.87	-15.04	-16.93	-16.41	-6.41	-10.55	-11.53	-10.69
SD	22.39	21.23	19.96	21.13	20.53	18.45	17.16	17.74
Median	-10.0	-15.0	-15.0	-15.0	-5.0	-10.0	-10.0	-10.0
Min	-100	-100	-90.0	-100	-55.0	-60.0	-75.0	-65.0
Max	75.0	50.0	33.8	60.0	80.0	40.0	35.0	35.0
Not Reported	2	1	3	5	2	0	1	0
Vision-Related Function (Q4, Q5, Q6, Q7, Q8, Q9)								
N	379	374	363	359	117	118	115	109
Mean	-16.07	-21.46	-22.82	-22.60	-14.08	-17.32	-20.92	-18.56
SD	29.80	27.93	28.22	27.30	29.94	27.49	27.66	28.92
Median	-12.5	-18.8	-18.8	-18.8	-6.3	-12.5	-16.7	-12.5
Min	-93.8	-100	-100	-100	-100	-100	-100	-100
Max	100.0	77.1	62.5	62.5	87.5	75.0	37.5	68.8
Not Reported	5	3	7	7	2	0	1	0
Environmental Triggers (Q10, Q11, Q12)								
N	370	367	358	353	114	116	113	106
Mean	-5.20	-7.27	-7.83	-7.41	-4.61	-7.26	-7.82	-7.70
SD	21.52	20.70	21.65	22.61	21.95	21.61	21.60	20.66
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min	-83.3	-100	-100	-100	-75.0	-100	-100	-75.0
Max	100.0	58.3	75.0	66.7	66.7	41.7	33.3	75.0
Not Reported	14	10	12	13	5	2	3	3
Overall Composite Score								
N	382	376	367	361	117	118	115	109
Mean	-11.87	-15.44	-16.66	-16.25	-8.48	-11.91	-13.60	-12.38
SD	20.29	19.39	19.38	19.73	20.02	18.01	17.18	18.38
Median	-10.4	-12.5	-13.3	-12.5	-6.2	-10.4	-10.7	-10.4
Min	-93.8	-93.8	-95.8	-100	-60.4	-66.7	-64.6	-62.5
Max	72.9	37.5	31.3	45.8	70.8	37.5	17.6	56.3
Not Reported	2	1	3	5	2	0	1	0

Each sub-scale is a summarization of some specific questions to the ODSI.

Patients in the iStent *inject* clinical study were asked about eye symptoms they experienced during the study. Some patients experienced worsening of some of these symptoms. This was reported for a small number of patients who had cataract surgery and iStent *inject* stents implanted, as well as for patients who only had cataract surgery. Many of these patients had other eye conditions that may have contributed to their symptoms. Because the questionnaire used was not developed with input from patients, the true rates

for symptoms may be different from the rates seen I this study. However, the rates of symptoms that got worse in the study are shown in **Table 17.**

Table 17: Rates of Worsening Eye Symptoms
2 Years after Surgery in the U.S. Clinical Study of iStent *inject*

	Cataract Surgery and iStent *inject* ***Number of Patients Out of 100***	**Cataract Surgery Alone** ***Number of Patients Out of 100***
Eyes that are sensitive to light	6	6
Eyes that feel gritty	2	2
Eyes that feel painful or sore	2	1
Blurry vision	2	2
Poor vision	1	2
Difficulty with reading	3	3
Difficulty with driving at night	1	7
Difficulty working with a computer or bank machine (ATM)	3	1
Difficulty watching TV	1	1
Eyes felt uncomfortable in windy conditions	3	2
Eyes felt uncomfortable in places or areas with low humidity (very dry)	2	2
Eye felt uncomfortable in areas that are air conditioned	2	1

Ocular symptoms were considered as "worsening" if they were rated as being two grades worse than at the beginning of the study

Table 18 shows eye symptoms that study patients reported experiencing "most of the time" or "all of the time" 2 years after the surgery, even if their symptoms did not worsen during the study.

Table 18: Rates of Eye Symptoms Occurring "most of the time" or "all of the time" 2 Years after Surgery in the U.S. Clinical Study of iStent *inject*

	Cataract Surgery and iStent *inject* ***Number of Patients Out of 100***	**Cataract Surgery Alone** ***Number of Patients Out of 100***
Eyes that are sensitive to light	10	12
Eyes that feel gritty	2	3
Eyes that feel painful or sore	1	1
Blurry vision	4	6
Poor vision	3	3
Difficulty with reading	6	6
Difficulty with driving at night	9	11
Difficulty working with a computer or bank machine (ATM)	5	3
Difficulty watching TV	1	2
Eyes felt uncomfortable in windy conditions	4	5
Eyes felt uncomfortable in places or areas with low humidity (very dry)	5	3
Eye felt uncomfortable in areas that are air conditioned	3	1

Symptoms were included if they were reported at 2 years as occurring "most of the time" or "all of the time," even if the symptoms did not worsen during the study or were related to conditions that were present before the study started.

C. In the iStent *inject* pivotal trial, at 24 months, the proportion of patients with medication-free diurnal IOP ≤ 18 mmHg was 63.2% n/N = 244/386 in the treatment group and 50.0% n/N = 60/119 in the control group (difference 13.2%; 95% CI 2.9%, 23.4%)[2].

D. In the iStent *inject* pivotal trial, mean observed unmedicated IOP was higher at baseline and lower at 24 months in the iStent *inject* group. IOP at baseline was 24.8 (SD 3.4) mmHg in the iStent *inject* group and 24.5 (SD 3.1) mmHg in the control group. Unmedicated IOP at 24 months was 17.1 mmHg (SD

[2] Based on proportional analysis using a non-responder imputation for missing data. Subjects without Month 24 medication-free diurnal IOP, or with IOP-related SSIs, loss of light perception or hypotony (IOP < 6 mmHg) associated with clinically significant findings prior to 24 months were treated as non-responders. iStent *inject* subjects with stent reposition or removal prior to 24 months were treated as non-responders.

3.6) at 24 months in the iStent *inject* group and 17.8 mmHg (SD 3.5) in the control group.[3]

Of the patients who were responders (e.g., 24-month unmedicated mean DIOP was reduced by ≥20% as compared with baseline in the absence of IOP-affecting surgery during the study), 84% of subjects in the iStent inject group (243/288) and 67% of subjects in the Control Group (49/73) were not using ocular hypotensive medication at 23 months. Responders are a subset of the Effectiveness Cohort.

E. In the iStent *inject* pivotal trial, 74.5% of patients in the iStent *inject* group (266/380 and 54.1% (59/118) of patients in the Control group without secondary surgical interventions (SSIs) or other events were not using ocular hypotensive medication at 23 months.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The iStent *inject* met its pivotal trial primary and secondary effectiveness endpoints.

B. Safety Conclusions

The risks of the iStent *inject* are based on data collected in the pivotal iStent *inject* clinical study conducted to support PMA approval as described above.

Device-related serious AEs include:

- 1 case (0.3%;1/386) of mild partial stent obstruction that did not require intervention

[3] Based on mean observed unmedicated IOP values from only those subjects with unmedicated IOP and without SSIs or other events (including loss of light perception or hypotony (IOP < 6 mmHg) associated with clinically significant findings).

Device-related non-serious intraoperative AEs include:

- 4 cases (1.0%; 4/386)) of 3 stents implanted
- 2 cases (0.5%; 2/386) of mild corneal abrasion and 1 case (0.3%; 1/386) of moderate corneal abrasion
- 2 cases (0.5%; 2/386) of 1 stent implanted
- 1 case (0.3%; 1/386) each of 2 stents implanted in same location and stent implanted in ciliary body

Non-serious postoperative AEs include:

- 23 cases (6.0%; 23/386) of stent obstruction, 3 (0.8%; 3/386) of which required laser
- 22 cases of any intraocular inflammation remaining or arising after the protocol's specified medication regimen is compete (5.7%; 22/386), of which 3 cases (0.8%) were chronic iritis
- 10 cases (2.6%; 10/386) of loss of BSCVA at least 10 letters at or after 3 months postoperative
- 7 cases (1.8%; 7/386) of focal goniosynechiae
- 4 cases (1.0%; 4/386) of deep stents
- 1 case (0.3%; 1/386) each of iris strand and ocular irritation
- 8 cases (2.1%; 8/386) of later IOP ≥10 mmHg over baseline

SSIs were needed in 5.4% (21/386) of iStent *inject* subjects during the study

The most common other clinical safety findings in the iStent *inject* arm included:

- Microhyphema (3.9%; 15/386)
- Goniosynechiae (7.7%; 30/386)
- Corneal endothelial pigment (0.8%; 3/386)

Notable operative parameters included:

- Need for a second injector (14.2%; 55/387) due to first injector did not deploy stent, stent not adequately seated in TM, poor visibility, stent dislodged during I/A.[4]
- Injector difficulty (18.3%; 71/387) due to injector did not deploy stent, stent not adequately seated in T, poor visibility, 2 stents implanted in same location.[5]

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. As such, the iStent *inject* Trabecular Micro-Bypass System pivotal trial achieved its primary

[4] Reports of use of a second injector and of stent implantation difficulty are not mutually exclusive. Further, the same reason could be reported for 1 eye in both categories.

[5] Reports of use of a second injector and of stent implantation difficulty are not mutually exclusive. Further, the same reason could be reported for 1 eye in both categories.

and secondary effectiveness endpoints. There were no cases of hypotony at 1 month or later, hypotony maculopathy, loss of light perception, endophthalmitis, choroidal hemorrhage or effusion, wound leak, flat anterior chamber (AC), or bleb complications - AEs anticipated with conventional incisional glaucoma surgery (i.e., tube or trabeculectomy). Further, there were no confirmed cases of stent dislocation, or surgical procedures to remove or reposition stents.

The probable risks of the device are also based on the data collected in a clinical study conducted to support PMA approval as described above. The most common safety issues related to the iStent *inject* Trabecular Micro-Bypass System were stent obstruction, inflammation (the majority of which were transient), goniosynechiae (nearly all of which were focal), and deep stents which could not be localized. Due to the relatively small size of the iStent *inject*, postoperative visualization of stents via gonioscopy or ultrasound biomicroscopy (UBM) was sometimes a challenge. The postoperative endothelial cell density findings were comparable in the iStent *inject* group and the control group.

Additional factors to be considered in determining probable risks and benefits for the iStent *inject* included:

- the iStent *inject* is a second-generation trabecular bypass, MIGS device.
- the iStent *inject* study is a prospective, randomized, controlled, multicenter study in which 505 subjects were randomized and followed for 24 months postoperatively. This PMA incorporates glaucoma medication washout, safety and effectiveness determination with 2-year follow-up, specular microscopy, and sample size which exceeded the sufficient number of subjects to have 95% probability of detecting AEs occurring at a rate of 1%.
- Of note, there was a very low percentage of major protocol deviations (0.002%) and high degree of subject accountability. Ninety-four percent (94%; 447/475) of subjects randomized (n = 475) completed the 24-month study follow-up period, which is significant given the age and co-morbidity associated with the study
- The overall safety profile of the iStent *inject* group was excellent and similar to that in the control group
- The sponsor proposes a surgeon training program that is reflected in the proposed product labeling
- Mild to moderate open angle glaucoma can also be managed with medication, lasers, and other incisional glaucoma surgeries. Conventional incisional glaucoma surgeries (i.e., tube or trabeculectomy) are typically reserved for more severe disease because it is marked with a turbulent postoperative course

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information summarized above, the data support that for the reduction of intraocular pressure observed in adult patients with mild to moderate open-angle glaucoma the probable benefits of the iStent *inject* outweigh the probable risks when used in conjunction with cataract surgery.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The iStent *inject* Trabecular Micro-Bypass System in conjunction with cataract surgery is an addition to the ophthalmologist's armamentarium to address mild to moderate primary open-angle glaucoma (POAG) which is not anticipated to preclude other options. Implanted in conjunction with cataract surgery, the iStent *inject* Trabecular Micro-Bypass System offers a safer surgical option with the aim of a reduction in IOP.

XIV. CDRH DECISION

CDRH issued an approval order on June 21, 2018. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study – Extended Follow-up of the Premarket Cohort Implanted with the iStent *inject*® Trabecular Micro-Bypass System: The study is a prospective, multicenter, observational study with no planned interventions to assess the long term safety in subjects who have completed participation in the IDE clinical trial (study protocol GC-008). The study is designed to evaluate the long-term rate of clinically relevant complications associated with iStent *inject*® placement and stability. The sample size will include 366 eyes of 366 patients. This is based on the number of patients implanted with GTS400(s) using the G2-M-IS injector system, completed 24 month follow-up in study Protocol GC-008 and will meet the study eligibility criteria. The subjects will be followed for 60 months post-randomization in the IDE trial. Annual follow-up will be at Months 36, 48 and 60.

   The primary safety endpoint is the rate of clinically relevant complications associated with iStent *inject*® Trabecular Micro-Bypass System placement and stability as determined at 60 months. Specific device-related complications include clinical sequelae resulting from device position including, but not limited to: secondary surgical intervention (SSI) to modify device position (e.g., repositioning or explantation); corneal endothelial touch by device; and corneal

edema leading to best spectacle corrected visual acuity (BSCVA) loss > 2 lines at the Month 60 visit, in comparison with preoperative BSCVA.

Other safety outcomes include 1) rate of occurrence of sight threatening adverse events including: persistent (at time of study exit) BSCVA loss ≥ 3 lines compared to best recorded BSCVA at any postoperative visit; endophthalmitis; corneal decompensation; retinal detachment; and severe choroidal hemorrhage or detachment or aqueous misdirection; 2) rate of ocular secondary surgical interventions (SSI); 3) rate of other adverse events including: increase from baseline IOP of ≥ 10 mmHg at any time ≥ 30 days postoperative; BSCVA loss ≥ 2 lines at Month 60 compared to screening; BSCVA loss ≥ 2 lines at Month 60 compared to best recorded BSCVA at any postoperative visit; and device movement, defined as a stent not visible in the original location, that does not result in clinically relevant complications as described above (e.g., SSI to modify device position, corneal endothelial touch by device, or corneal edema leading to BSCVA loss > 2 lines at the Month 60 visit compared to preoperative BSCVA), and that is not attributable to any one or more of the following: variations in gonioscopic, optical coherence tomography (OCT) or ultrasound biomicroscopy (UBM) viewing angle or illumination; changes in angle anatomy due to concomitant findings such as resolution of hyphema; or changes in anterior chamber depth development of focal peripheral anterior synechiae (PAS).

2. OSB Lead PMA Post-Approval Study – iStent *inject*® Trabecular Micro-Bypass System New Enrollment PAS: The study is a prospective, non-randomized, multicenter, single arm, new enrollment post approval study to evaluate the rate of clinically relevant complications associated with iStent *inject* placement and stability as determined at 36 months in the postmarket setting compared to the pre-specified performance target of 2%. The study population is adults who have mild to moderate primary open angle glaucoma (POAG) in the study eye and are undergoing cataract surgery in that eye. A total of 358 eyes of 358 subjects will be enrolled at up to 30 sites, to ensure that a minimum of 250 subjects will be available at 36 months to test the hypothesis that the probability of having clinically relevant complications associated with iStent *inject*® placement and stability during the 36-month follow-up period is less than or equal to 2%. Post-operative follow-up will occur at Day 1, Week 1, and Months 1, 3, 6, 12, 24, and 36.

   The primary safety endpoint is the rate of clinically relevant complications associated with iStent *inject*® placement and stability as determined at 36 months. Specific device-related complications include clinical sequelae resulting from device position including, but not limited to: secondary surgical intervention (SSI) to modify device position (e.g., repositioning or explantation), corneal endothelial touch by device, and corneal edema leading to Best Spectacle-Corrected Visual Acuity (BSCVA) loss > 2 lines at the Month 36 visit, in comparison with preoperative BSCVA.

Other safety endpoints include 1) Rate of occurrence of sight-threatening adverse events including persistent (at time of study exit) BSCVA loss ≥ 3 lines compared to best recorded BSCVA at any postoperative visit, endophthalmitis, corneal decompensation, retinal detachment, and severe choroidal hemorrhage or detachment or aqueous misdirection; 2) Rate of ocular secondary surgical interventions (SSI); and 3) Other adverse events including increase from baseline IOP of ≥ 10 mmHg at any time ≥ 30 days postoperative, BSCVA loss ≥ 2 lines at Month 36 compared to screening, BSCVA loss ≥ 2 lines at Month 36 compared to best recorded BSCVA at any postoperative visit, and device movement, defined as a stent not visible in the original location, that does not result in clinically relevant complications as described above (e.g., SSI to modify device position, corneal endothelial touch by device, or corneal edema leading to BSCVA loss > 2 lines at the Month 36 visit compared to preoperative BSCVA), and that is not attributable to any one or more of the following: variations in gonioscopic, Optical Coherence Tomography (OCT) or Ultrasound Biomicroscopy (UBM) viewing angle or illumination, changes in angle anatomy due to concomitant findings such as resolution of hyphema, changes in anterior chamber depth, or development of focal peripheral anterior synechiae.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.