I. GENERAL INFORMATION

Device Generic Name:	Intraocular Pressure Lowering Implant
Device Trade Name:	Glaukos iStent® Trabecular Micro-Bypass Stent (Models: GTS-100R, GTS-100L) and inserter (GTS-100i)
Device Procode:	OGO
Applicant's Name and Address:	Glaukos Corporation 26051 Merit Circle, Suite 103 Laguna Hills, CA 92653
Date(s) of Panel Recommendation:	July 30, 2010
PMA Number:	P080030
Date of Notice of Approval:	June 25, 2012
Expedited:	Not applicable

II. INDICATIONS FOR USE

The iStent® Trabecular Micro-Bypass Stent System, Models GTS100R and GTS100L, is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma who are currently treated with ocular hypotensive medication.

III. CONTRAINDICATIONS

The iStent® Trabecular Micro-Bypass Stent is contraindicated under the following circumstances or conditions:

- In eyes with primary angle-closure glaucoma, or secondary angle-closure glaucoma, including neovascular glaucoma, because the device would not be expected to work in such situations
- 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® Trabecular Micro-Bypass Stent System (Models GTS100R and GTS 100L) labeling.

V. DEVICE DESCRIPTION

The Glaukos iStent® Trabecular Micro-Bypass Stent, Models GTS100R and GTS100L, (iStent or stent) is a one-piece, heparin-coated, titanium, L-shaped implant that comes pre-loaded in a disposable, single-use applicator for insertion into the eye through a temporal cataract surgery incision following successful cataract extraction and intraocular lens implantation. Once inside the eye, the inserter is passed across the anterior chamber, and the stent is implanted through the nasal trabecular meshwork and into Schlemm's canal. When properly implanted, the iStent is intended to create a bypass through the trabecular meshwork to Schlemm's canal to improve aqueous outflow through the natural physiologic pathway.

The stent is 1.0 mm in length, 0.33 mm in height, with a snorkel length of 0.25 mm, and a snorkel bore diameter of 120µm (Figure 1).

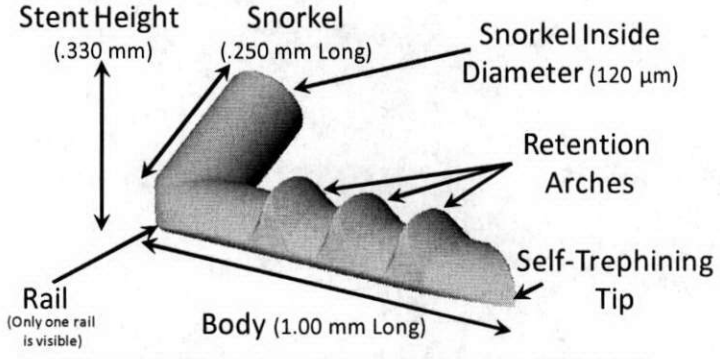

Figure 1. iStent; front view of right stent GTS100R

The iStent has an "L"-shaped structure with a snorkel (inlet) on the short side that resides in the anterior chamber and opens to the half-pipe body that resides in Schlemm's canal. The closed side of the body (**Figure 1**) sits against the inner wall of Schlemm's canal. The retention arches on the closed side of the body serve to securely fixate the device in Schlemm's canal. The open half-pipe part of the body (**Figure 2**) is against the outer wall in order to access collector channels. The rails are the edges of the open half-pipe. **Figure 2** shows a view of the stent in **Figure 1**, rotated 180 degrees, to display the open half-pipe of the stent body. The device is heparin-coated for purposes of lubrication for self-priming to establish initial flow.

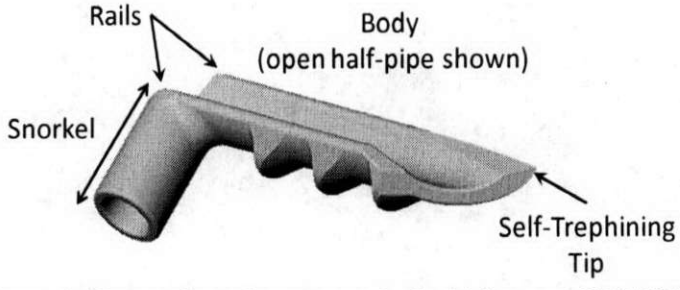

Figure 2. iStent; view of open stent body (right stent GTS100R)

Two models of the stent are available, the GTS100L and the GTS100R. The two models are identical except the bodies face opposite directions in order to facilitate nasal stent

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placement. Model GTS100L is designed for the left eye, and Model GTS100R is designed for the right eye. A "stand-alone" (without the stent) version of the inserter, Model GTS100i, is also available. This inserter is provided as a single-use, disposable device for intraocular removal or retrieval of the device, should it be necessary.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

There are several other alternatives for the treatment of mild and moderate open-angle glaucoma in patients who are already being treated with ocular hypotensive medication(s), including:

- Continuing or adding additional IOP-lowering medications, such as topical eye drops or systemic IOP-lowering drugs
- Laser treatment, such as argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT)
- Other surgeries, such as non-penetrating deep sclerectomy and trabeculectomy.

Each alternative has its own advantages and disadvantages. A patient should fully discuss the alternatives with his/her physician in order to select the alternative that is most appropriate for the patient's needs.

VII. MARKETING HISTORY

The iStent® Trabecular Micro-Bypass Stent has been marketed in European Union countries, Canada, and Armenia.

The iStent® Trabecular Micro-Bypass Stent has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse reactions associated with implantation of the iStent® Trabecular Micro-Bypass Stent include: inadvertent perforation of sclera, significant hyphema, inadvertent loss of vitreous/vitrectomy performed, choroidal hemorrhage or effusion, clinically significant iris damage, prolonged anterior chamber collapse, endothelial or iris touch, iris incarceration to the wound, posterior capsular bag rupture, flat anterior chamber, wound leak, loss of best corrected visual acuity (BCVA), difficulty or inability to implant the stent, premature stent release, stent malposition, stent malfunction, stent obstruction by iris, vitreous, fibrous overgrowth, fibrin, blood, etc., inflammation (anterior or posterior uveitis, sterile hypopyon, or pupillary membrane formation), late stent dislocation, infection (endophthalmitis), bleeding (vitreous hemorrhage, subconjunctival hemorrhage), corneal complications (corneal edema or opacification), retinal complications (dialysis, flap tears, retinal detachment, macular hole, or proliferative vitreoretinopathy), choroidal complication (massive choroidal hemorrhage), hypotony, unplanned surgical intervention, chronic pain, IOL dislocation, cystoid macular edema, pupillary block, worsening glaucoma, and elevated IOP requiring treatment with oral or intravenous medications or with surgical intervention.

The occurrence of many of these events may involve the necessity of secondary (additional) surgical intervention.

For the specific adverse events that occurred in the pivotal clinical study, please see Section X.D.1 below.

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IX. SUMMARY OF PRECLINICAL STUDIES

Table 1: Summary of Preclinical Studies

	Test	Purpose	Acceptance Criteria	Results
Stent	**Cytotoxicity:**			
	Inhibition Of Cell Growth, 9 Point Assay	Determine whether stent inhibits unwanted cell growth	No cell growth	Pass
	Minimum Essential Media Elution Test	Determine whether stent is toxic to surrounding tissue	No cell lysis or toxicity	Pass
	Genotoxicity:			
	Bacterial Reverse Mutation Study	Determine whether stent promotes unwanted cell mutation	No mutagenic changes	Pass
	Mouse Bone Marrow Micronucleus Study	Determine whether stent is toxic or mutagenic	No toxicity or mutagenic effects	Pass
	In Vitro Chromosomal Aberration Study	Determine whether stent induces chromosomal aberrations	No chromosomal aberrations induced	Pass
	Other:			
	Intraocular Irritation Study in the Rabbit	Determine whether stent causes irritation	No evidence of irritation	Pass
	Guinea Pig Maximization Sensitization Study	Determine whether stent delays dermal contact sensitization	No evidence of delayed dermal contact sensitization	Pass
	Muscle Implantation in the Rabbit (2, 6, and 12 Weeks)	Determine whether stent causes any significant reactions	No significant reaction	Pass
	Acute Systemic Toxicity in the Mouse	Determine whether stent is systemically toxic	No evidence of systemic toxicity	Pass
	United States Pharmacopeia Material-mediated Pyrogen Study	Determine whether stent causes fever	Non-pyrogenic	Pass
	Heparin performance	Determine the necessary quantity of heparin coating to induce wetting of titanium	Induce droplets of water on surface to expand	0.9µg
	Physical Stability	Determine whether the stent can withstand incubation	Section 4.1.4 of ANSI Z80.27:2001	Pass
	Structural Integrity	Determine whether the stent can withstand the forces commonly exerted upon it	Maximum calculated force does not exceed known physical properties	Pass
	Sterilization validation	Determine whether the method is capable of sterilizing the stent	AAMI TIR27: 2001	Pass
	Accelerated shelf-life studies	Determine the expected	Meet the release criteria post	3 years

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	Test	Purpose	Acceptance Criteria	Results
		shelf-life of final packaged products after sterilization	accelerated aging	
Inserter	**Cytotoxicity:**			
	Minimum Essential Media Elution Test	Determine whether inserter is toxic to surrounding tissue	No cell lysis or toxicity	Pass
	Other:			
	Guinea Pig Maximization Sensitization Study	Determine whether inserter delays dermal contact sensitization	No evidence of delayed dermal contact sensitization	Pass
	Acute Systemic Toxicity in the Mouse	Determine whether inserter is systemically toxic	No evidence of systemic toxicity	Pass
	Intraocular Irritation Study in Rabbits	Determine whether inserter causes irritation	No irritation or toxicity	Pass
	Sterilization validation	Determine whether the method is capable of sterilizing the inserter	AAMI TIR27: 2001	Pass
	Accelerated shelf-life studies	Determine the expected shelf-life of final packaged products after sterilization	Meet the release criteria post accelerated aging	3 years

A. Laboratory Studies

1. Biocompatibility Testing

The biocompatibility testing outlined in the table below was performed on the stent (or representative samples of the finished device) and the patient-contacting portion of the inserter in accordance with the International Organization for Standardization (ISO) standard 10993-1.

Table 2: Biocompatibility Testing

TEST	RESULTS
Stent	
Cytotoxicity:	
Inhibition Of Cell Growth, 9 Point Assay	No cell growth
Minimum Essential Media Elution Test	No cell lysis or toxicity
Genotoxicity:	
Bacterial Reverse Mutation Study	No mutagenic changes
Mouse Bone Marrow Micronucleus Study	No toxicity or mutagenic effects
In Vitro Chromosomal Aberration Study	No chromosomal aberrations induced
Other:	
Intraocular Irritation Study in the Rabbit	No evidence of irritation
Guinea Pig Maximization Sensitization Study	No evidence of delayed dermal contact sensitization
Muscle Implantation in the Rabbit (2, 6, and 12 Weeks)	No significant reaction
Acute Systemic Toxicity in the Mouse	No evidence of systemic toxicity
United States Pharmacopeia Material-mediated	Non-pyrogenic

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TEST	RESULTS
Pyrogen Study	
Inserter	
Cytotoxicity:	
Minimum Essential Media Elution Test	No cell lysis or toxicity
Other:	
Guinea Pig Maximization Sensitization Study	No evidence of delayed dermal contact sensitization
Acute Systemic Toxicity in the Mouse	No evidence of systemic toxicity
Intraocular Irritation Study in Rabbits	No irritation or toxicity
United States Pharmacopeia Material-mediated Pyrogen Study	Non-pyrogenic

2. Physico-Chemical Testing

There is an extensive history of titanium use in medical devices. Therefore, tests for extraction in aqueous and in organic solvents and for hydrolytic stability were not performed on the device, since they were considered unnecessary. In addition, the device's titanium material contains no monomers and is not subject to hydrolytic degradation.

Testing related to the heparin coating was performed. To demonstrate that the heparin coating promotes wetting of the titanium surface of the stent, photos were taken of water droplets on heparin-coated and non-coated titanium blocks with the same surface finish as the stents. The photos indicated that the water droplets expanded more on the heparin-coated than on the non-coated blocks. In order to estimate the amount of heparin coating on the stents, heparin was extracted from coated stents with organic solvent and the amount of heparin was estimated using UV spectrophotometry. The average amount of heparin per stent was estimated to be 0.9 micrograms. Fourier transform infrared spectroscopy is performed on all lots of heparin used for coating the stents to ensure consistency of the heparin. The infrared spectrum of an initial lot of heparin was designated by Glaukos as the "standard" against which all lots are compared.

3. Physical and Mechanical Testing

The stent was subjected to the physical and mechanical requirements identified in Section 4.1 of American National Standards Institute (ANSI) standard Z80.27-2001. Tests for surface quality, dimensions, physical stability, pressure/flow characteristics, and structural integrity were performed.

a. Physical Stability: Glaukos performed an *in vivo* physical stability test to evaluate the functional and dimensional stability of the iStent. A total of 4 gamma sterilized stents were placed into glass vials filled with distilled water, and then the vials were submerged in a beaker of water for 14 days at a temperature of 37 $\pm$ 2 °C in accordance with Section 4.1.4 of ANSI Z80.27:2001. Visual inspection at 10x and dimensional measurements were performed at baseline and after 14 days. The stents underwent visual inspection for pits, scratches, corrosion, and cracking, and presence of heparin was

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confirmed after 14 days by eosin y dye. Dimensional inspection was performed for the outer snorkel diameter. The results of the dimensional inspection showed that the outer snorkel diameter measurements remained the same before and after incubation. The results of the visual inspection demonstrated that the surface finish on the incubated stents maintained the same quality as prior to incubation. The data also show that the coating on the stents remains intact after incubation.

b. Structural Integrity: A simulation was undertaken to evaluate the stress levels during the highest anticipated load conditions for the stent, which is constructed of titanium (type 6Al 4V). From published data, the yield strength of titanium type 6Al 4V is approximately 120,000 psi (pounds per square inch), and the ultimate tensile strength is approximately 130,000 psi.

Primary loading of the stent occurs during clamping in the inserter jaws. Smaller loads are also exerted on the stent by the tissue during implantation into the trabecular meshwork. For the purposes of this analysis, these lower loads are considered negligible. After implantation, the stent has no mating parts, and is contained within the soft tissues of the trabecular meshwork.

For the finite element model, the stent snorkel and 4-segment inserter collet were accurately modeled using the computer-aided design database, CAD Pro-E, for the parts, and meshed in a finite element solver (MSC Software Corporation). The outer sleeve was treated as a rigid body, and, therefore, not meshed in the solver. A spring force of 0.3 pounds corresponding to the 0 .088-inch diameter spring used in the inserter was applied to the outer sleeve, and a friction coefficient of 0.3 was applied to the sliding interface. Stresses at the four slotted tube/snorkel contact point run approximately 10,000 psi, based on this modeling.

The anticipated stress level of 10,000 psi is well below the published 120,000 psi yield strength of the titanium device material (safety factor of 12). Therefore, catastrophic material failure, such as cracking or fracture, is unlikely to occur at the stress levels encountered during use of this device. Furthermore, the stent is machined in a single piece from monolithic titanium. There are no joints, attachments, mating parts, or dissimilar materials.

4. Microbiological Testing

A sterilization validation for the stent and inserter (i.e., the stent pre-loaded on the inserter) was performed by Glaukos to validate the irradiation dose and to confirm that a sterility assurance level (SAL) of 10^{-6} was achieved. The sterilization validation and dose audit verifications were performed in accordance with AAMI TIR27: 2001 – "Substantiation of 25kGy as a Sterilization Dose – Method VDmax." The acceptance criteria for the sterilization validation were as follows:

- The verification dose experiment sterility test must pass, meaning that there

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must be no more than one positive sterility results out of the ten samples tested.

- The actual verification dose must be within ± 10% of the determined verification dose.
- The Bacteriostasis/Fungistasis testing must demonstrate that the product does not inhibit growth when challenged with a low number of microorganisms.
- Limulus Amebocyte Lysate (LAL) testing (an inhibition/enhancement test per the current United States Pharmacopeia) demonstrates the product is within acceptable limits for endotoxins (0.5 EU/ml).

The results of the validation confirmed that the gamma sterilization process delivers a minimum SAL of 10^{-6}, and all of the above acceptance criteria were met. In addition, the test method for bacterial endotoxin testing has been validated.

5. Shelf Life & Shipping Tests

Accelerated shelf-life studies were performed for the stent/inserter packaging configuration to allow extrapolation of testing intervals under accelerated conditions to intervals at normal storage conditions. For microbial barrier testing, the accelerated conditions involved storage at a specified temperature and with a relative humidity of at least 60%. The corresponding real-time shelf life was calculated by multiplying the studied time period by 1.8(Ta-To)/10 where Ta is the accelerated temperature (45° Celsius (C) + 5° C) and To is the typical storage temperature (25° Celsius (C) + 5° C).

Product stability testing was performed for the stent and the inserter, and package integrity testing was performed for the sterile barrier.

For product stability, the following tests were performed:

- Visual inspection for appearance (discoloration or physical distortion of product and package components).
- Visual inspection of labeling: Adhesive detachment and legibility of all print on the labels.
- Measurement of stent release force to ensure that the force required to separate the stent from the inserter after depressing the trigger is not excessive.
- Measurement of the gripping force of the inserter jaws.
- Presence of heparin via dye testing to ensure that heparin remains on the stent throughout the product shelf life.
- Measurement of stent critical dimensions per specification drawings, and measurement of all critical dimensions for both the inner and outer packaging trays.
- Evaluation of heparin wettability using titanium coupons, i.e., the ability of the coating to maintain its hydrophilic properties, which relate to priming ability.

For package integrity, the following tests were performed:

- ISTA 3A Transportation test/simulation on all package integrity products
- Seal strength test and dye penetration or bubble leak test.

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

X. SUMMARY OF CLINICAL STUDIES

The safety and effectiveness of the device was assessed through several clinical trials conducted within and outside of the U.S. In addition, limited European postmarket clinical data and some clinical data through the Canadian Special Access Program were collected. The safety information from a total of 364 patients implanted with the iStent (with 306 iStent eyes followed through 12 months) was taken into consideration.

The pivotal IDE study and the key safety and effectiveness information derived from this study are summarized below.

A. Study Design

The pivotal IDE study had three arms. The first two arms comprised a prospective, randomized, open-label, multi-center, controlled clinical trial conducted at 27 U.S. investigational sites. Those subjects randomized (1:1) to the treatment group were to undergo cataract surgery with iStent implantation, and those randomized to the control group were to undergo cataract surgery alone. Subjects in the randomized population were treated from April 13, 2005 through June 28, 2007, and the database for this PMA reflected data in the database as of May 17, 2010. The randomized population consisted of 240 eyes of 239 subjects (117 treatment eyes of 116 subjects and 123 control eyes of 123 subjects). The third arm was a non-randomized cohort of an additional 50 subjects at 10 sites included for safety evaluation.

1. Eligibility Criteria

   Patients were screened for eligibility including undergoing an initial screening exam, and informed consent was obtained from those who met screening criteria (including medicated IOP of less than or equal to 24 mmHg) and were interested in participating in the study. If a subject satisfied all inclusion and exclusion criteria and the investigator believed that the subject would also meet the unmedicated IOP value of ≥ 22 mmHg and ≤ 36 mmHg, the subject was enrolled and advised to begin a washout-period for the ocular hypotensive medications in the study eye. After the washout period, the subject returned for the baseline evaluation. Subjects with IOP from 22 mmHg to 36 mmHg off of medications in the study eye were then scheduled for surgery.

   a. Inclusion Criteria

      Enrollment into the pivotal study was limited to patients who met the below inclusion criteria. All inclusion criteria applied to the study eye only except where indicated.

      - Subjects were to have been diagnosed with mild to moderate open-angle glaucoma (OAG). This included primary open-angle glaucoma (POAG)

and the secondary open-angle glaucomas pseudoexfoliative glaucoma (PXG) and pigmentary glaucoma (PG).

Diagnosis of mild to moderate OAG was based on the following functional and structural parameters:

A. C:D Ratio: Given the requirement for early stage glaucomatous disease, the subject's cup-disc ratio (C:D) must have been enlarged consistent with glaucoma, but still ≤ 0.8. Additionally, the subject had to qualify by having a visual field defect consistent with glaucoma and meeting the criteria described in "B" OR by having at least one of the characteristic nerve abnormalities as described in "C" (below).

B. Visual Field criteria (VF): In case of visual field defect, the following criteria must have been met:
   - No severe nasal steps worse than 4 continuous clustered points
   - No more than 3 clustered points with sensitivity less than 15dB within 15 degrees from the fixation point
   - No other evidence at clinical examination of moderate to advanced nerve fiber bundle defects (i.e., Bjerrum scotoma).

C. Characteristic nerve abnormalities consistent with glaucoma: One or more of the following was acceptable for diagnosis:
   - Segmental loss of neuroretinal rim (notching)
   - Drance disc hemorrhage (splinter hemorrhage)
   - Nerve fiber layer loss (as observed with an ophthalmoscope)
   - Pseudo pit of the disc
   - Visible laminar dots
   - Optic nerve abnormalities determined by confocal scanning imaging Heidelberg Retina Tomograph (HRT)
   - Findings on polarimetry consistent with early glaucoma such as a wedge-shaped defect connecting to the optic nerve head with values at or below the 5th percentile as evidenced on the deviation map, any parameter below the 5th percentile, or the Nerve Fiber Indicator (NFI) > 35 (GDx).
   - Findings on optical coherence tomography (OCT) of retinal nerve fiber layer (RNFL) thickness outside of the normal range consistent with clinical evaluation of the optic nerve and RNFL.

- Best corrected visual acuity (BCVA) of 20/40 or worse with medium Brightness Acuity Tester (BAT) and clinically significant cataract eligible for phacoemulsification
- Subject taking at least one ocular hypotensive medication, but not more than three medications, with a stable prescription for at least 2 months and able to undergo a washout (study eye only).
- Medicated IOP of ≤ 24 mmHg at screening evaluation

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- Unmedicated IOP ≥ 22 mmHg and ≤ 36 mmHg at baseline visit, after washout
- Gonioscopy confirming normal anatomy for cataract eyes (excluding peripheral anterior synechiae (PAS), rubeosis, or other angle abnormalities that can lead to improper placement of the stent)
- Able and willing to attend follow-up visits for two years postoperatively
- Able and willing to sign informed consent

b. Exclusion Criteria

Subjects were excluded from the study for the following reasons:

- Under age 18
- Angle closure glaucoma
- Unmedicated IOP of < 22 or > 36 mmHg (baseline visit); medicated IOP > 24 mmHg (screening visit)
- Any subject such that the washout period would put at risk their visual fields or for whom the unmedicated IOP after washout would be expected to exceed the upper limit (> 36 mmHg).
- Secondary glaucoma, except pseudoexfoliative and pigmentary; no neovascular, uveitic, or angle recession glaucoma
- Prior glaucoma surgery of any type (argon laser trabeculoplasty, trabeculectomy, viscocanalostomy, FDA-approved shunts, collagen implants, cyclo destructive procedures, etc.). Prior iridectomy is acceptable as long as the reason for the procedure was NOT angle closure.
- Cloudy corneas where opacity will inhibit gonioscopic view of the nasal angle
- Elevated episcleral venous pressure from history of active thyroid orbitopathy, carotid-cavernous fistula, Sturge Weber syndrome, orbital tumors, or orbital congestive disease.
- Chronic ocular inflammatory disease
- Significant prior trauma to eye including chemical burn
- Existing PAS (peripheral anterior synechiae) where PAS is located near enough to the potential implant site to cause problems initially or subsequently secondary to progression of PAS.
- Glaucoma associated with vascular disorders
- Previous refractive procedures that prevent accurate IOP measurements (e.g., PRK, LASIK)
- Prior cataract surgery
- Split fixation by Visual Field
- Abnormal anterior segment
- Proliferative or pre-proliferative diabetic retinopathy
- Monocular subjects or subjects with BCVA in fellow eye worse than 20/200
- Known corticosteroid responder

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- Occludable appearing angles
- Previous retinal detachment surgery
- Fellow eye actively enrolled
- Subject already participating in another clinical trial.

If the subject experienced cataract surgery complications during the operative procedure, the subject would be exited from the study and a Study Summary Form would be completed. If no complications occurred, the subject would continue with regularly scheduled study follow-up.

2. Exam Schedule

The examination schedule for the study was as follows: screening evaluation, baseline exam, operative procedure, 3-7 hours postoperative, and then 1 day, 1-2 weeks, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months postoperatively.

Table 3: Activities Conducted During Clinical Study

Activities	Screening	Baseline	Op	Follow-up Evaluation								
				3-7 Hrs	1 Day	1-2 Wk	1 Mo	3 Mo	6 Mo	12 Mo	18 Mo	24 Mo
Informed Consent	X											
Randomization		X										
Ophthalmology Exam	X											
Ocular Medical History	X	X										
Ocular Medication Assessment	X	X			X	X	X	X	X	X	X	X
History/Demographics		X										
Visual Field	X (New or History)	X (New)							X	X		X
C:D Ratio	X					X			X	X		X
Slit-lamp Exam	X				X	X	X	X	X	X	X	X
Visual Acuity (ETDRS)		X					X	X	X	X	X	X
Visual Acuity (Snellen)	X											
Visual Acuity (pinhole)					X	X						
Manifest Refraction	X	X					X	X	X	X	X	X
Fundus exam/Nerve Abnormalities	X					X			X	X		X
IOP[2]	X	X		X	X	X	X	X	X	X	X	X
Gonioscopy[1]	X					X	X	X	X	X	X	X
Goniophotography (optional)							X					X
Pachymetry		X								X		X
Surgical Procedure			X									
Videotape (if available)			X									
Observations Recorded		X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment			X	X	X	X	X	X	X	X	X	X

[1] Only required for Group 1 subjects where stent implanted

[2] If IOP spike is observed immediately post-op or on day 1, it should be reassessed on post-op day 2 or 3, in addition to the scheduled visits.

The key time point was at 12 months postoperatively.

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3. Clinical Endpoints

The primary effectiveness endpoint was IOP ≤ 21 mmHg without use of ocular hypotensive medication at 12 months. The secondary effectiveness endpoint was IOP reduction from baseline of ≥ 20% without use of ocular hypotensive medication at 12 months. For each of these endpoints, the proportion of subjects in the randomized treatment group who met the endpoint was compared to the proportion in the randomized control group who met the endpoint after excluding outcomes following secondary surgical intervention (including stent repositioning, stent explantation/replacement, implantation of multiple stents, IOL explantation/replacement, trabeculectomy and other glaucoma surgeries, and iridoplasty for stent obstruction, and based upon an intent-to-treat (ITT) principle.

ITT analysis requires the inclusion of all randomized subjects based upon the group to which they were assigned, whether or not they actually received that study treatment. Those subjects that missed the 12-month evaluation were considered non-responders for purposes of these analyses.

With regard to safety, anticipated and unanticipated adverse events were reported for all subjects, randomized and non-randomized, enrolled in the study.

B. Accountability

Randomized Subjects

A total of 240 eyes of 239 subjects were enrolled in the randomized portion of the pivotal study. At the time of the PMA submission, the randomized phase of the IDE study has been completed with 24-month follow-up of all subjects.

One hundred and seventeen (117) eyes of 116 subjects were randomized to the treatment group (cataract surgery + iStent implantation). One-hundred and sixteen (116) randomized treatment group eyes underwent surgery. One-hundred and eleven (111) of these eyes had successful implantation of the iStent. Of these, 106 completed the 12-month postoperative visit. One hundred and four (104) completed the 24-month visit.

One hundred and twenty-three (123) subjects were randomized to the control group (cataract surgery only). One hundred and seventeen (117) of these underwent surgery. One hundred and twelve (112) subjects were evaluated at the 12-month visit. One hundred and seven (107) were seen at the 24-month visit.

Non-randomized Subjects

Fifty (50) subjects were enrolled in the non-randomized portion of the pivotal study. Forty-eight (48) subjects underwent cataract surgery with iStent implantation. Forty-six (46) subjects were successfully implanted with the iStent. Forty-four (44) subjects were seen at the 12-month visit and 44 subjects were seen at the 24-month visit.

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Demographics and Baseline Characteristics

The demographics and some baseline characteristics of the pivotal study population are summarized in Table 4 below.

Table 4: Demographics and Baseline Characteristics

	Randomized Group		Non-Randomized Group	Total	P-value[2]	P-value[3]
	Cataract Surgery with iStent® N=116[1]	Cataract Surgery Only N=123	Cataract Surgery with iStent® N=50	N=289[1]		
Age (Years)						
N	116	123	50	289	0.3088	0.7185
Mean	73.96	72.88	73.49	73.42		
Std. Dev.	7.66	8.66	7.79	8.11		
Minimum	53.39	48.92	54.93	48.92		
Maximum	88.57	88.52	87.52	88.57		
<60	4 (3.45%)	12 (9.76%)	3 (6.00%)	19 (6.57%)	0.2472	0.4808
60 to <70	33 (28.45%)	31 (25.20%)	10 (20.00%)	74 (25.61%)		
70 to <80	49 (42.24%)	53 (43.09%)	26 (52.00%)	128 (44.29%)		
≥80	30 (25.86%)	27 (21.95%)	11 (22.00%)	68 (23.53%)		
Gender						
Male	46 (39.66%)	52 (42.28%)	19 (38.00%)	117 (40.48%)	0.6951	0.8643
Female	70 (60.34%)	71 (57.72%)	31 (62.00%)	172 (59.52%)		
Race						
American Indian or Alaska Native	1 (0.86%)	1 (0.81%)	0 (0%)	2 (0.69%)	0.8974	0.0534
Asian	1 (0.86%)	0 (0%)	1 (2.00%)	2 (0.69%)		
Black or African American	15 (12.93%)	19 (15.45%)	3 (6.00%)	37 (12.80%)		
Native Hawaiian or Pacific Islander	1 (0.86%)	0 (0%)	0 (0%)	1 (0.35%)		
Hispanic or Latino	16 (13.79%)	15 (12.20%)	16 (32.00%)	47 (16.26%)		
White	82 (70.69%)	88 (71.54%)	30 (60.00%)	200 (69.20%)		
Medicated IOP (mmHg) at Screening						
N	117	123	50	290	0.1035	0.2115
Mean (SD)	18.70 (3.28)	18.04 (3.03)	18.01 (3.24)	18.30 (3.18)		
Min, Max	9.50, 24.00	12.00, 24.00	11.00, 24.00	9.50, 24.00		
Unmedicated IOP (mmHg) at Baseline						
N	117	123	50	290	0.5172	0.6900
Mean (SD)	25.20 (3.46)	25.50 (3.72)	24.98 (2.93)	25.29 (3.49)		
Min, Max	21.00, 36.00	21.50, 36.00	22.00, 35.00	21.00, 36.00		
Eyes using IOP-lowering Medications at Screening						
N	117	123	50	290	0.0693	0.2578
One Medication	71 (60.68%)	73 (59.35%)	34 (68.00%)	178 (61.38%)		
Two Medications	28 (23.93%)	41 (33.33%)	13 (26.00%)	82 (28.28%)		
Three medications	18 (15.38%)	9 (7.32%)	3 (6.00%)	30 (10.34%)		

1. N for age, gender, and race reflects the number of subjects. N for the other parameters reflects the number of eyes; 117 eyes of 116 subjects were randomized to the Cataract Surgery with iStent® group.
2. Randomized Stent Group vs. Cataract Surgery Only Group – Fisher's Exact tests for categorical variables and two-sample t-tests for continuous variables.
3. Randomized Stent Group vs. Non-Randomized Stent Group – Fisher's Exact tests for categorical variables and two-sample t-tests for continuous variables.

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There were no statistically significant differences between the randomized iStent group and the randomized control group or between the randomized iStent group and the non-randomized iStent group for the characteristics listed in the table.

All eyes had primary open-angle glaucoma, except for four eyes in the randomized treatment group and three in the randomized control group with pigmentary glaucoma and seven in each of these groups with pseudoexfoliative glaucoma. Because of the low number of eyes in these latter two subgroups, the safety and effectiveness of the device in these two subgroups could not be established.

Additional baseline characteristics of the pivotal study eyes are summarized in Table 5 below.

Table 5: Additional Baseline Characteristics

	Randomized Group		Non-Randomized Group
	Cataract Surgery with iStent® N=117 Eyes	**Cataract Surgery Only N=123 Eyes**	**Cataract Surgery with iStent® N=50 Eyes**
Visual Field, Mean Deviation			
n	115	121	47
Mean	-3.75	-3.74	-3.78
Std. Dev.	3.03	3.86	3.84
Minimum	-14.21	-16.27	-18.52
Maximum	3.25	12.72	0.28
Visual Field, Pattern Standard Deviation			
n	110	112	46
Mean	2.89	2.79	2.48
Std. Dev.	1.79	1.90	1.61
Minimum	1.15	1.10	1.13
Maximum	11.20	10.38	10.23
Pachymetry (µm)			
n	117	123	48
Mean	550	548	547
Std. Dev.	43	37	42
Minimum	403	462	433
Maximum	735	642	688

N > n means missing values.

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C. Safety and Effectiveness Results

1. Safety Results

a. Intraoperative Adverse Events

Out of the 160 eyes (112 from the randomized and 48 from the non-randomized treatment groups) in which iStent implantation was attempted, there were 23 intra-operative complications that were directly attributable to the iStent, as summarized in Table 6 and discussed below:

Table 6: Intra-Operative Stent-Specific Adverse Events

N = 160	n (%)
Iris touched by the device	11 (7%)
Failure to implant stent	3 (2%)
Endothelium touched	2 (1%)
Stent malposition	2 (1%)
Stent released into anterior chamber - successful removal and replacement	1 (0.6%)
Multiple attempts to successfully implant stent	1 (0.6%)
Anterior chamber collapse	1 (0.6%)
Iris damage	1 (0.6%)
Ocular pain during insertion	1 (0.6%)

In the randomized treatment eyes, the intra-operative adverse events related directly to iStent implantation included the following:

- iStent implantation was not successful in one subject due to poor visualization of the angle as a result of moderate arcus and due to shallow angle;
- Eight (8) eyes experienced iris touch with the iStent (one case involved unsuccessful iStent implantation),
- One experienced endothelial touch,
- One experienced stent release into the anterior chamber, requiring removal of the stent and insertion of another, and
- One had a malpositioned stent (in the scleral spur), leading the investigator to insert a second additional stent at the time of surgery.

In the non-randomized treatment eyes, intra-operative complications related directly to iStent implantation included the following:

- In two cases, stent implantation was unsuccessful after several attempts due to "poor visibility". These subjects were exited from the study after surgery.
- Four additional subjects experienced intraoperative complications:
  - One required 4 attempts to insert the device and experienced anterior chamber collapse, iris touch by the device, and pain during insertion.
  - In one subject, the stent was implanted in the incorrect location (behind the iris insertion between the ciliary body and the sclera) and iris touch and damage were reported due to the stent being

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inadvertently inserted through a small iridodialysis. This subject complained of early postoperative pain that resolved.
- One subject was reported to have had the corneal endothelium touched by the device.
- One subject was reported to have had the iris touched by the device.

All four of these additional intraoperative complications had resolved with BCVA of 20/40 or better at the last study visit.

Complications related to cataract extraction and IOL implantation were reported in 9 eyes in the randomized population (5 treatment and 4 control):

- inadvertent loss of vitreous or vitrectomy: 5 treatment eyes:
  - four were exited from the study
  - one was implanted with the stent (considered a protocol violation)

- inadvertent loss of vitreous or vitrectomy: 3 control eyes
  - all three were exited following the surgery.

- torn IOL haptic and IOL exchange at the time of surgery: 1 control eye
  - this one eye was not exited and was counted as a protocol violation.

There were no subjects in the non-randomized cohort who experienced complications related to cataract surgery.

b. Postoperative Adverse Events

Table 7 below summarizes the postoperative adverse events that occurred during the course of the pivotal IDE study, where N is the number of eyes that underwent surgery (116 randomized treatment group eyes, 117 randomized control group eyes, and 48 non-randomized treatment group eyes). Of the 157 successful iStent implantations (111 in the randomized treatment group and 46 in the non-randomized treatment group) there were 12 reports of postoperative adverse events that were clearly stent-related – 7 cases of stent obstruction and 5 cases of stent malposition, as indicated in Table 7 below.

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Table 7: Postoperative Ocular Adverse Events

Adverse Events	Randomized Treatment Group [1] (Cataract Surgery with iStent®) N = 116 n (%)	Randomized Control Group [2] (Cataract Surgery Only) N = 117 n (%)	Non-Randomized Group [3] (Cataract Surgery with iStent®) N = 48 n (%)	Combined Treatment Group [1] + [3] (Cataract Surgery with iStent®) N = 164 n (%)
Anticipated early postoperative event				
Early postop corneal edema	9 (7.8%)	11 (9.4%)	2 (4.2%)	11 (6.7%)
Early postop anterior chamber cells	4 (3.4%)	2 (1.7%)	2 (4.2%)	6 (3.7%)
Early postop corneal abrasion	3 (2.6%)	2 (1.7%)	1 (2.1%)	4 (2.4%)
Early postop corneal striae	2 (1.7%)	1 (0.9%)	1 (2.1%)	3 (1.8%)
Early postop discomfort	1 (0.9%)	2 (1.7%)	0 (0%)	1 (0.6%)
Early postop subconjunctival hemorrhage	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Early postop superficial punctate keratitis	0 (0%)	2 (1.7%)	0 (0%)	0 (0%)
Early postop blurry vision	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Early postop floaters	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Early postop anterior chamber inflammation	0 (0%)	0 (0%)	1 (2.1%)	1 (0.6%)
Early postop corneal erosion	0 (0%)	0 (0%)	1 (2.1%)	1 (0.6%)
Early postop pain	0 (0%)	0 (0%)	1 (2.1%)	1 (0.6%)
Any BCVA loss of at least 1 line at or after the three month visit	**8 (6.9%)**	**12 (10.3%)**	**3 (6.3%)**	**11 (6.7%)**
Posterior capsular opacification	7 (6.0%)	12 (10.3%)	4 (8.3%)	11 (6.7%)
Stent obstruction by iris, vitreous, fibrous overgrowth, fibrin, blood, etc.	**5 (4.3%)**	**0 (0%)**	**2 (4.2%)**	**7 (4.3%)**
Blurry vision or visual disturbance	4 (3.4%)	8 (7=6.8%)	2 (4.2%)	6 (3.7%
Elevated IOP - other	**4 (3.4%)**	**5 (4.3%)**	**1 (2.1%)**	**5 (3.0%)**
Stent malposition	**3 (2.6%)**	**0 (0%)**	**2 (4.2%)**	**5 (3.0%)**
Subconjunctival hemorrhage	2 (1.7%)	2 (1.7%)	0 (0%)	2 (1.2%)
Epiretinal membrane	2 (1.7%)	1 (0.9%)	4 (8.3%)	6 (3.7%)
Drusen	2 (1.7%)	0 (0%)	0 (0%)	2 (1.2%)
Iris atrophy	2 (1.7%)	0 (0%)	0 (0%)	2 (1.2%)
Iritis	1 (0.9%)	6 (5.1%)	0 (0%)	1 (0.6%)
Conjunctival irritation due to hypotensive medication	1 (0.9%)	3 (2.6%)	0 (0%)	1 (0.6%)
Disc hemorrhage	1 (0.9%)	3 (2.6%)	0 (0%)	1 (0.6%)
Elevated IOP requiring treatment with oral or intravenous medications or with surgical intervention	**1 (0.9%)**	**3 (2.6%)**	**0 (0%)**	**1 (0.6%)**
Allergic conjunctivitis	1 (0.9%)	2 (1.7%)	1 (2.1%)	2 (1.2%)
Dry eye	1 (0.9%)	2 (1.7%)	0 (0%)	1 (0.6%)
Macular edema	**1 (0.9%)**	**2 (1.7%)**	**0 (0%)**	**1 (0.6%)**
Cystoid macular edema	**1 (0.9%)**	**1 (0.9%)**	**1 (2.1%)**	**2 (1.2%)**
Worsening of glaucoma	1 (0.9%)	1 (0.9%)	1 (2.1%)	2 (1.2%)
Allergy to cosmetics	1 (0.9%)	1 (0.9%)	0 (0%)	1 (0.6%)
Age related macular degeneration	1 (0.9%)	0 (0%)	1 (2.1%)	2 (1.2%)
Uveitis	**1 (0.9%)**	**0 (0%)**	**1 (2%)**	**2 (1.2%)**
Bleeding (vitreous hemorrhage or persistent & non-preexisting hyphema)	**1 (0.9%)**	**0 (0%)**	**0 (0%)**	**1 (0.6%)**
Blepharospasm	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Corneal edema	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Dysesthesia and/or photophobia	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Endo pigment	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Eye splash injury	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Eyelid bruise due to fall	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Metallic particle on iris	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Mild throbbing pain	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Periorbital hematoma due to fall	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)

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Adverse Events	Randomized Treatment Group [1] (Cataract Surgery with iStent®) N = 116 n (%)	Randomized Control Group [2] (Cataract Surgery Only) N = 117 n (%)	Non-Randomized Group [3] (Cataract Surgery with iStent®) N = 48 n (%)	Combined Treatment Group [1] + [3] (Cataract Surgery with iStent®) N = 164 n (%)
Possible bacterial conjunctivitis	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Seasonal allergies	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Subconjunctival hemorrhage secondary to aspirin	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Transient hypotony	**1 (0.9%)**	**0 (0%)**	**0 (0%)**	**1 (0.6%)**
Mild pain	0 (0%)	5 (4.3%)	0 (0%)	0 (0%)
Posterior vitreous detachment	0 (0%)	4 (3.4%)	2 (4.2%)	2 (1.2%)
Foreign body sensation	0 (0%)	4 (3.4%)	0 (0%)	0 (0%)
Rebound inflammation from tapering steroids	0 (0%)	2 (1.7%)	0 (0%)	0 (0%)
Blepharoconjunctivitis	0 (0%)	1 (0.9%)	1 (2.1%)	1 (0.6%)
Worsening of age related macular degeneration	0 (0%)	1 (0.9%)	1 (2.1%)	1 (0.6%)
Anterior chamber + 1 cells (at 1 month) requiring treatment	**0 (0%)**	**1 (0.9%)**	**0 (0%)**	**0 (0%)**
Burning due to dry eye	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Carotid artery disease	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Choroidal detachment	**0 (0%)**	**1 (0.9%)**	**0 (0%)**	**0 (0%)**
Choroidal tubercle	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Conjunctivitis	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Endophthalmitis	**0 (0%)**	**1 (0.9%)**	**0 (0%)**	**0 (0%)**
Episcleritis	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Intermittent tearing	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Keratitis sicca	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Lesion on eyelid	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Macular hole	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Macular traction	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Poor near vision	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Postoperative refractive error	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Proliferative diabetic retinopathy	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Segmental loss of neuroretinal rim	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Superficial punctate keratitis	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Wound leak	**0 (0%)**	**1 (0.9%)**	**0 (0%)**	**0 (0%)**
Blepharitis	0 (0%)	0 (0%)	2 (4.2%)	2 (1.2%)
Vitreous floaters	0 (0%)	0 (0%)	2 (4.2%)	2 (1.2%)
Iris incarceration	**0 (0%)**	**0 (0%)**	**1 (2.1%)**	**1 (0.6%)**
Keratitis	0 (0%)	0 (0%)	1 (2.1%)	1 (0.6%)
Periorbital swelling	0 (0%)	0 (0%)	1 (2.1%)	1 (0.6%)
Unwanted eyelid sensation	0 (0%)	0 (0%)	1 (2.1%)	1 (0.6%)
Vitreous condensations	0 (0%)	0 (0%)	1 (2.1%)	1 (0.6%)

There were 6 reports of secondary surgical interventions (included Table 8 below) that were clearly related to iStent placement in the randomized and non-randomized treatment subjects, including:

- 3 eyes requiring stent repositioning,
- 1 case of stent removal and replacement,
- 1 report of laser iridoplasty to resolve stent obstruction, and
- 1 report of stent obstruction that was resolved by using an Nd:YAG laser.

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TABLE 8: SECONDARY SURGICAL INTERVENTIONS — ADVERSE EVENTS

Secondary Surgical Intervention[1] Adverse Events	Randomized Treatment Group [1] (Cataract Surgery with iStent®) N = 116 n (%)	Randomized Control Group [2] (Cataract Surgery Only) N = 117 n (%)	Non-Randomized Group [3] (Cataract Surgery with iStent®) N = 48 n (%)	Combined Treatment Group [1] + [3] (Cataract Surgery with iStent®) N = 164 n (%)
Paracentesis[2]	31 (26.7%)	34 (29.1%)	12 (25.0%)	43 (26.2%)
Nd:YAG laser capsulotomy	7 (6.0%)	11 (9.4%)	7 (14.6%)	14 (8.5%)
Stent repositioning	3 (2.6%)	0 (0%)	0 (0%)	3 (1.8%)
Punctal cautery/punctual plugs	1 (0.9%)	3 (2.6%)	0 (0%)	1 (0.6%)
Trabeculoplasty	1 (0.9%)	2 (1.7%)	0 (0%)	1 (0.6%)
Nd:YAG laser for stent obstruction	1 (0.9%)	0 (0%)	1 (2.1%)	2 (1.2%)
Focal argon laser photocoagulation	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Stent removal and replacement	1 (0.9%)	0 (0%)	0 (0%)	1 (0.6%)
Deep sclerectomy/sclerostomy	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
IOL removal and replacement	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
LASIK	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Pupilloplasty	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Vitrectomy	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Wound resuture due to wound leak	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Iris reposition	0 (0%)	0 (0%)	1 (2.1%)	1 (0.6%)

1 Including intervention for elevated IOP

2 Paracentesis included the paracenteses performed at 5-7 hours after IOL implantation.

2. Effectiveness Results

a. Primary Effectiveness Outcome

As indicated in the table below, 68% of subjects in the treatment group (combined cataract and iStent® implantation) met the primary endpoint (ITT, non-responder analysis) of IOP ≤ 21 mm Hg without ocular hypotensive medications at 12 months postoperatively. In comparison, only 50% of subjects in the control group (cataract surgery only) met the primary endpoint. This treatment difference of 18% in favor of the iStent® group was statistically significant (p = 0.004).

TABLE 9: IOP ≤ 21 MMHG WITHOUT OCULAR HYPOTENSIVE MEDICATIONS AT 12 MONTHS

Analysis Population and Imputation Method	Cataract Surgery with iStent® N=116 (%)	Cataract Surgery Only N=123 (%)	P-value[1]
ITT Using Non-Responder Analysis	68%	50%	0.004

1. Two-sided Z-test

The evaluation of effectiveness at 24 months postoperatively was not pre-specified. At 24 months postoperatively, there did not appear to be a difference between groups for the primary effectiveness outcome, as indicated in Table 10 below.

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TABLE 10: IOP ≤ 21 MMHG WITHOUT OCULAR HYPOTENSIVE MEDICATIONS AT 24 MONTHS

Analysis Population and Imputation Method	Cataract Surgery with iStent® N=116 (%)	Cataract Surgery Only N=123 (%)	Difference (90% Confidence Interval)
ITT Using Non-Responder Analysis	56%	46%	9.7% (-0.9%, 20.3%)

b. Secondary Effectiveness Outcome

The secondary endpoint in the GC-003 pivotal trial was the proportion of patients with IOP reduced ≥ 20% from baseline without ocular hypotensive medications at 12 months postoperatively. As indicated in the table below, in the iStent® treatment group, 64% of subjects implanted met this outcome (ITT, non-responder analysis) compared to 47% in the cataract control group. This treatment difference of 17% was statistically significant (p =0.01).

TABLE 11: IOP REDUCTION ≥ 20% WITHOUT OCULAR HYPOTENSIVE MEDICATIONS AT 12 MONTHS

Analysis Population and Imputation Method	Cataract Surgery with iStent® N=116 (%)	Cataract Surgery Only N=123 (%)	P-value[1]
mITT Using Non-Responder Analysis	64%	47%	0.01

1. Two-sided Z-test.

As stated above, the evaluation of effectiveness at 24 months postoperatively was not pre-specified. At 24 months postoperatively, there did not appear to be a difference between groups for the secondary effectiveness outcome, as indicated in Table 12 below.

TABLE 12: IOP REDUCTION ≥ 20% WITHOUT OCULAR HYPOTENSIVE MEDICATIONS AT 24 MONTHS

Analysis Population and Imputation Method	Cataract Surgery with iStent® N=116 (%)	Cataract Surgery Only N=123 (%)	Difference (90% Confidence Interval)
ITT Using Non-Responder Analysis	49%	40%	9.3% (-1.2%, 19.8%)

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The pivotal study was not masked, and the decision to treat subjects with IOP-lowering "rescue" medications after surgery was left to the physicians' discretion. About 11.1% of the rescued subjects in the randomized treatment group had IOP lower than 21 mmHg

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prior to receiving the rescue medication, while about 26.8% of the rescued subjects in the randomized control group had IOP lower than 21 mmHg prior to receiving rescue medication. After the Ophthalmic Devices Panel of the Medical Devices Advisory Committee met on July 30, 2010 to discuss the pre-market application (PMA) P080030 for this device (further discussed below), an additional study was performed. Because FDA was concerned that more control group subjects than treatment group subjects may have tended to receive rescue medications, thereby, artificially producing more failures in the control group than the treatment group, the applicant was asked to conduct a study whereby masked, independent, glaucoma experts reviewed the relevant data from the randomized portion of the pivotal study to determine whether IOP-lowering medication should have been re-introduced. The results of this study could not prove nor rule out bias.

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

A. Panel Meeting Recommendation

At an advisory meeting held on July 30, 2010, the Ophthalmic Devices Panel of the Medical Devices Advisory Committee met on July 30, 2010 to discuss the pre-market application (PMA) P080030. The Panel voted 7 yes and 1 no on whether there was reasonable assurance of safety. They voted 6 yes and 2 no on the question of whether there was reasonable assurance of effectiveness, and they voted 7 yes and 1 no on whether the benefits outweighed the risks. The transcript of the advisory panel meeting may be found at:
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/ophthalmicdevicespanel/ucm225539.pdf.

B. FDA's Post-Panel Action

After the Ophthalmic Devices Panel of the Medical Devices Advisory Committee met on July 30, 2010 to discuss the pre-market application (PMA) P080030 for this device, an additional study was performed. Because FDA was concerned that more control group subjects than treatment group subjects may have tended to receive rescue medications, thereby, artificially producing more failures in the control group than the treatment group, the applicant was asked to conduct a study whereby masked, independent, glaucoma experts reviewed the relevant data from the randomized portion of the pivotal study to determine whether IOP-lowering medication should have been re-introduced. The results of this study could not prove nor rule out bias.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Sixty-eight percent (68%) of subjects in the treatment group (combined cataract and iStent® implantation) and 50% of subjects in the control group (cataract surgery only) met the primary endpoint (IOP $\leq$ 21 mm Hg without ocular hypotensive medications at 12 months postoperatively). Sixty-four percent (64%) of subjects in the treatment group and 47% of the subjects in the control group met the secondary

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effectiveness endpoint (IOP reduced ≥ 20% from baseline without ocular hypotensive medications at 12 months postoperatively). The treatment differences of 18% and 17% respectively in favor of the treatment group were statistically significant. A subsequent study was performed to address the concern that lack of masking may have artificially lead to more failures in the control than the treatment group. The results of this study could neither prove nor rule out bias.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical studies conducted to support PMA approval as described above. For most adverse events, it was impossible to determine whether the event was caused by the stent and its implantation or to the cataract surgery and implantation of an intraocular lens, since both procedures were performed at the same time. Out of 160 eyes in the pivotal study in which iStent implantation was attempted, there were 23 intraoperative adverse events that could be directly attributed to the stent, which included:

- iris touch
- failure to implant the stent
- endothelial touch
- stent malposition
- multiple attempts to implant the stent
- iris damage
- ocular pain during insertion.

Two of these events were serious. During one case of multiple attempts at implanting the stent, there was anterior chamber collapse, and during another case, the stent was released into the anterior chamber.

Out of 157 eyes with successful iStent implantation, there were 12 reports of postoperative adverse events that could be directly attributed to the stent – 7 cases stent obstruction and 5 cases of stent malposition. Out of these cases of obstruction and malposition, there were 6 reports of secondary surgical interventions attempting to correct these problems.

C. Benefit-Risk Conclusions

The probable benefit of the device is based on data collected in a clinical study conducted to support PMA approval as described above. The pivotal study showed that the probable benefit of implantation of a single iStent in combination with cataract surgery is that it will lower intraocular pressure in a greater percentage of people than will cataract surgery alone. At 12 months postoperatively, 68% of subjects in the treatment group (combined cataract and iStent® implantation) and 50% of subjects in the control group (cataract surgery only) had IOP ≤ 21 mm Hg without ocular hypotensive medications, and 64% of subjects in the treatment group and 47% of the subjects in the control group had their IOP reduced ≥ 20% from baseline without ocular hypotensive medications. The mean un-medicated IOP at

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baseline was about 25 mmHg for both the treatment group and the control group. While the evaluation of effectiveness at 24 months postoperatively was not pre-specified, there did not appear to be a difference between groups for the effectiveness outcomes at 24 months.

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

- A study was performed to address the concern that lack of masking may have artificially lead to more failures in the control than the treatment group. The results of this study could neither prove nor rule out bias.
- The risks of entering the eye to implant the iStent are mitigated by the stent being indicated for implantation only during another intraocular surgery to restore a patient's vision, cataract surgery.
- There are several other alternatives for the treatment of mild and moderate open-angle glaucoma in patients who are already being treated with ocular hypotensive medication(s), including:
    - Continuing or adding additional IOP-lowering medications, such as topical eye drops or systemic IOP-lowering drugs.
    - Laser treatment, such as argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT).
    - Other surgeries, such as non-penetrating deep sclerectomy and trabeculectomy.

  However, chronic use of medications is problematic due to issues with compliance, and highly effective surgical alternatives also have significant risks. A relatively low risk surgical alternative, such as the iStent, is desirable.

In conclusion, given the available information above, the data support that for use in conjunction with cataract surgery for the reduction of IOP in adult patients with mild to moderate open-angle glaucoma who are currently treated with ocular hypotensive medication the probable benefit outweighs the probable risks.

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 additional IOP-lowering benefit that the iStent should provide to some mild to moderate open-angle glaucoma patients undergoing cataract surgery above the IOP-lowering benefit they would have achieved with cataract surgery alone outweighs the additional risks of implanting the iStent above the risks of cataract surgery alone.

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XIV. CDRH DECISION

CDRH issued an approval order on June 25, 2012. The final conditions of approval cited in the approval order are described below.

1. *Extended Follow-up of IDE Cohort Study*: The purpose of the study is to assess the long-term safety of the Glaukos® iStent® Trabecular Micro-Bypass Stent Models GTS100R and GTS100L in subjects enrolled in Glaukos IDE Study GC-003. Both the device group and control group will be followed for five years. Device subjects received the Glaukos iStent in conjunction with cataract surgery and controls subjects received cataract surgery alone. A remaining 255 patients from the original cohort of 290 patients enrolled for the GC-003 study are eligible to participate in this post-approval study.

   The main safety endpoint is the rate of sight-threatening adverse events at five years. Sight-threatening adverse events include: BCVA loss ≥ 3 lines, endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment and aqueous misdirection. The difference in the sight-threatening adverse event rates at 5 years between the treatment group and control group will be calculated and the corresponding one-sided 90% confidence limit will be provided based on normal distribution approximation.

   In addition, data on the following safety measures will be collected: postoperative ocular adverse events, IOP levels, medication use, best spectacle-corrected visual acuity (BSCVA), VF measurements and pachymetry, findings from slit-lamp, fundus and gonioscopic measurements, and loss of best spectacle corrected visual acuity of ≥ 1 line (≥ 5 letters) at ≥ 3 months postoperative.

2. *New Enrollment Study*: This will be a prospective, randomized, concurrently controlled, parallel group, multicenter study to assess the long-term safety of the Glaukos® iStent® Trabecular Micro-Bypass Stent Model GTS100 R and GTS100L in conjunction with cataract surgery. The treatment group will receive implantation of one stent per study eye in conjunction with cataract surgery. The control group will receive cataract surgery only. The study will include subjects with mild to moderate open-angle glaucoma, who will be enrolled in 20 to 45 sites. A total of 360 subjects (one eye per subject) will be enrolled and randomized with a 1:1 ratio, 180 will be randomly assigned to stent implantation in conjunction with cataract surgery and 180 will undergo cataract surgery only. Assuming a 20% loss of follow-up over 5 years, 288 subjects (or 144 per group) will be available for the main endpoint evaluation at 5 years.

   The primary safety endpoint is the sight-threatening adverse events. The rate of sight-threatening adverse events over a five year postoperative period will be compared between the treatment and control group. In addition, data will be collected on: intraoperative and postoperative ocular adverse events, findings from IOP,

BSCVA, VF, pachymetry, and specular microscopy measurements; findings from slit-lamp, fundus and gonioscopic measurements.

The effectiveness outcomes include IOP reduction ≥ 20% vs. baseline IOP without ocular hypotensive medication, and IOP ≤ 18 mmHg without ocular hypotensive medication at 24 months. The rate of these effectiveness outcomes will be compared between the treatment and control groups.

3. *Registry Study*: This will be a prospective, single-arm, multicenter registry of subjects implanted with GTS100 stents. A total of 500 consecutive subjects that receive implantation of GTS100 stents will be recruited at a maximum of 20 sites in the U.S. Subjects will be followed for three years from the date of implantation, to monitor the sight-threatening events that include BCVA loss ≥ 3 lines vs. screening, endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment, and aqueous misdirection. Other ocular adverse events such as increase in IOP of ≥ 10 mmHg vs. screening at any time postoperative or loss of best spectacle corrected visual acuity of ≥ 1 line (≥ 5 letters) vs. screening at ≥ 3 months postoperative will also be assessed. Additional safety events of interest include findings from IOP, best spectacle corrected visual acuity, visual field, and pachymetry, and findings from optic nerve head imaging and gonioscopic examination

   The rate of sight-threatening adverse events at each visit will be calculated. The Kaplan-Meier (K-M) method will be used to estimate the sight-threatening adverse event rate at three year postoperative. The corresponding 95% confidence interval will also be provided. For other adverse events the Kaplan-Meier (K-M) method will also be used.

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

XV. APPROVAL SPECIFICATIONS

Directions for Use: See the device labeling.

Hazards to health from use of the device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

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