Glaukos® Corporation iStent *inject*® W Trabecular Micro-Bypass System

Instructions for Use

DIRECTIONS FOR USE TABLE OF CONTENTS

1. DEVICE DESCRIPTION

The iStent *inject*® W Trabecular Micro-Bypass System Model G2-W 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 360 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.

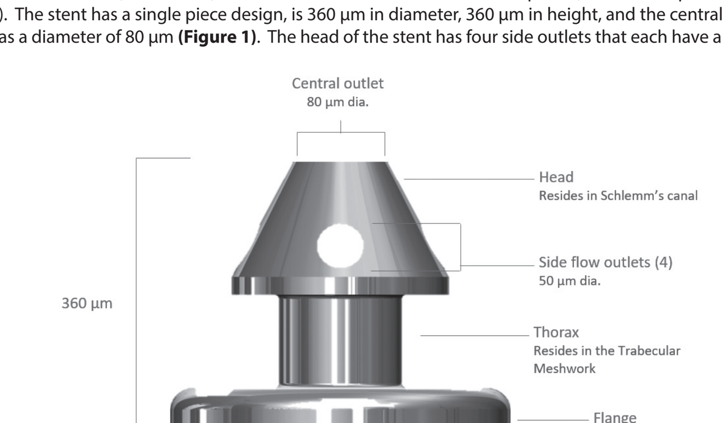

Figure 1. iStent *inject* W Stent Dimensions

The iStent *inject* W stent has a rear flange which resides in the anterior chamber, and 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 the left and right eye **(Figure 2)**. Two preloaded intraocular stents are provided in the injector **(Figures 3a & 3b)**.

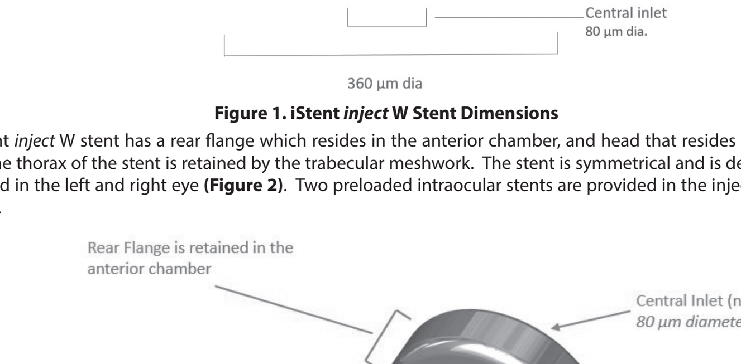

Figure 2. iStent *inject* W Model G2-W Stent

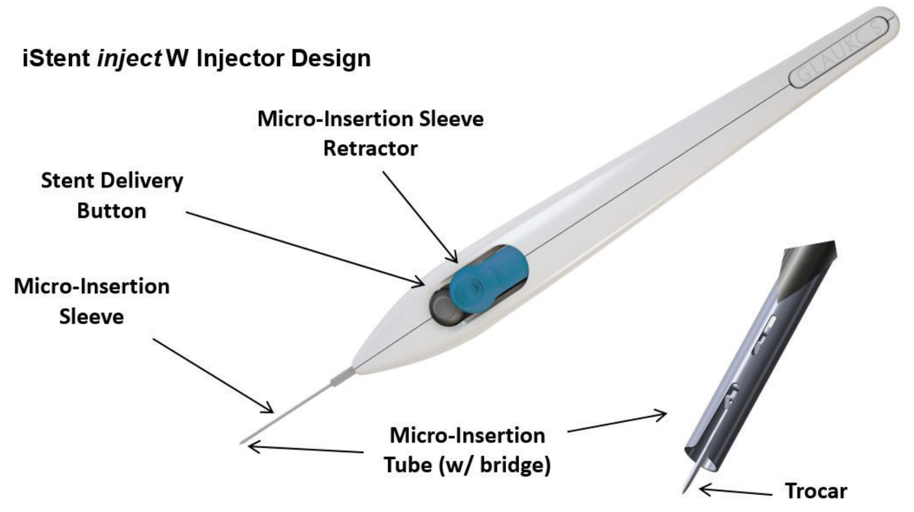

Figure 3a. iStent *inject* W G2-W Injector Design

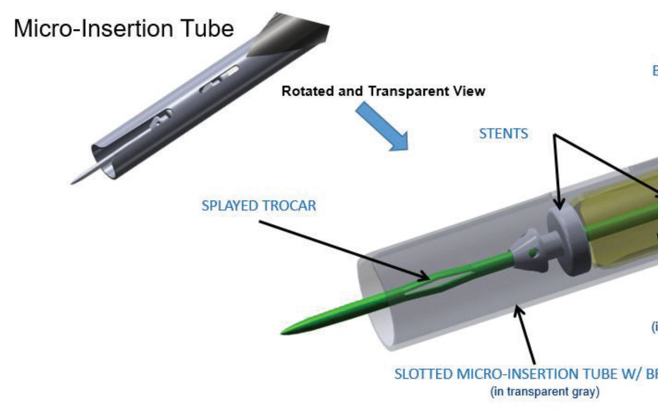

Figure 3b. iStent *inject* W G2-W Injector Distal End

When properly implanted, the iStent *inject* W 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.

Data from the clinical study of the Model G2-M-IS system, a prior iteration of the iStent *inject* W Model G2-W System, was used to support the safety and effectiveness of the G2-W system (see Section 13, "iStent *inject* G2-M-IS System – Pivotal Clinical Trial Results", below). The G2-W stents include a wider proximal end in the anterior chamber of 360 µm, rather than 230 µm for Model G2-M-IS.

2. INDICATIONS FOR USE

The iStent *inject* W Trabecular Micro-Bypass System Model G2-W 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.

3. CONTRAINDICATIONS

The iStent *inject* W Trabecular Micro-Bypass System Model G2-W 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

4. WARNINGS

1. The following conditions may prohibit sufficient visualization of the angle required for safe and successful stent implantation: corneal haze, corneal opacity, or any other conditions that may inhibit the gonioscopic view in the intended implant location.
2. The surgeon should perform a slit lamp gonioscopy examination prior to taking a patient to surgery to exclude congenital anomalies of the angle, including peripheral anterior synechiae (PAS), rubeosis, and any other angle abnormalities that could lead to improper placement of the stent and pose a hazard.
3. Patients with peripheral iridotomies are at risk of stent dislocation to the posterior chamber and related sequelae.
4. The iStent *inject* W is intended for implantation in conjunction with cataract surgery, which may impact corneal health. Therefore, caution is indicated in eyes with evidence of corneal compromise (e.g., corneal guttae or low endothelial cell density) or with risk factors for corneal compromise following cataract surgery (e.g., advanced age, severe nuclear sclerosis).
5. Non-clinical testing has demonstrated that the iStent *inject* W is MR Conditional. Please see the "MRI SAFETY INFORMATION" section at the end of this document on conditions for safe scanning.

5. PRECAUTIONS

1. The surgeon should inform the patient that the stent is MR Conditional (as noted on their Patient ID card), and if the patient needs to undergo an MRI, they should let their doctor know they have an iStent *inject* W stent implanted in their eye.
2. After the surgery, the surgeon should give the patient the Patient ID card (enclosed in the iStent *inject* W packaging) with the appropriate information filled in, and should advise the patient to keep the card in a safe place, e.g., his or her wallet, for future reference. The surgeon should advise the patient that this Patient ID card contains important information related to the iStent *inject* W and that the card should be shown to their current and future health care providers.
3. The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. If intraocular pressure is not adequately maintained after surgery, the surgeon should consider an appropriate additional therapy to reduce intraocular pressure.
4. The safety and effectiveness of the iStent *inject* W system has not been established as an alternative to the primary treatment of glaucoma with medications. The effectiveness of this device has been demonstrated only in patients with mild to moderate open-angle glaucoma who are undergoing concurrent cataract surgery for visually significant cataract.
5. The safety and effectiveness of the iStent *inject* W system has not been established in patients with the following circumstances or conditions which were not studied in the pivotal trial:
   - In children
   - In eyes with significant prior trauma
   - In eyes with abnormal anterior segment
   - In eyes with chronic inflammation
   - In glaucoma associated with vascular disorders
   - In pseudophakic patients with glaucoma
   - In uveitic glaucoma
   - In eyes with prior incisional glaucoma surgery or cilioablative procedures
   - In eyes with prior laser trabeculoplasty (LT) with selective LT within 90 days prior to screening or prior argon laser trabeculoplasty (ALT) at any time
   - In patients with medicated intraocular pressure greater than 24 mmHg
   - In patients with unmedicated IOP less than 21 mmHg nor greater than 36 mmHg after "washout" of medications
   - For implantation of more or less than two stents
   - After complications during cataract surgery, including but not limited to, severe corneal burn, vitreous removal/vitrectomy required, corneal injuries, or complications requiring the placement of an anterior chamber IOL
   - When implantation has been without concomitant cataract surgery with IOL implantation for visually significant cataract
   - In patients with pseudoexfoliative glaucoma or pigmentary glaucoma, or in patients with other secondary open-angle glaucomas.
6. The stent is comprised of implant grade titanium (Ti6-Al-4V-ELI) with a stearalkonium heparin coating. The total amount of heparin is estimated to be less than 0.9 microgram per stent, or approximately 0.01 to 0.02 units.
7. The surgeon should be careful to avoid contact with the cornea and iris during stent implantation in order to minimize sequelae associated with device-cornea touch, stent obstruction and/or iritis.

6. ADVERSE REACTIONS

Refer to the Pivotal Clinical Trial Results section for the adverse events that occurred in the pivotal clinical trial. Additional 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.

7. INSTRUCTIONS FOR USE

Cataract Surgery

1. Cataract surgery with IOL implantation should be performed first followed by implantation of the iStent *inject* W.
2. The stent implantations are designed for nasal placement; therefore, it is suggested that surgery is performed from the temporal side of the head.
3. An intracameral miotic can be injected to deepen the angle after cataract surgery prior to placement of the iStent *inject* W stent.
4. To mitigate difficulty with patient movement or non-compliance, consider using a peri-bulbar or retro-bulbar block.

Stent Implantation

a. Prepare for gonioscopy by turning the patient head away by approximately 35° and the scope toward surgeon by approximately 35° (70° total).
b. Inspect angle with a gonioprism to ensure that a good view is available at the nasal implant location.
c. Place the gonioprism on the cornea and position the patient and surgical microscope as needed to visualize the trabecular meshwork, through the gonioprism, on the nasal side of the eye. Focus on the landmarks in the angle of the eye **(Figures 4a & 4b)**. Look up from the iris root to find the scleral spur (white line). Then look for Schwalbe's line (white line) down from the cornea. The trabecular meshwork (typically a red/brown line) is between the scleral spur and Schwalbe's line. Schlemm's canal is behind the trabecular meshwork.

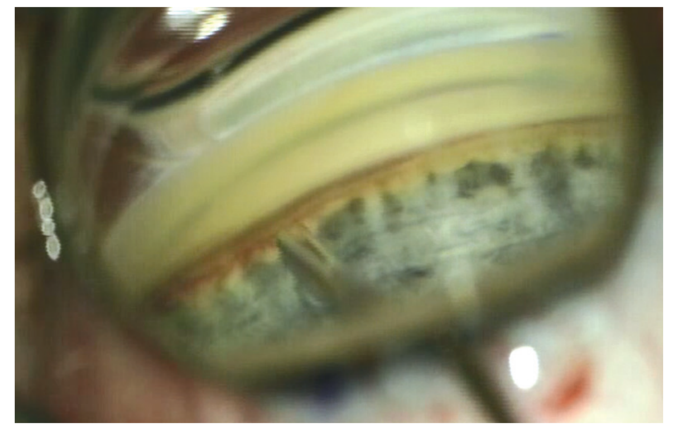

Figure 4a. iStent *inject* W Implant Site

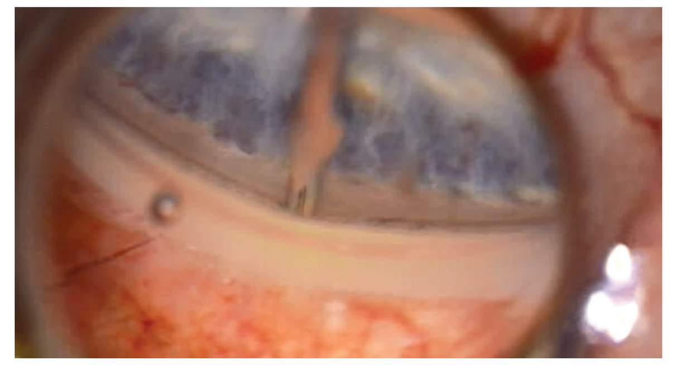

Figure 4b. iStent *inject* W Implant Site

d. After visualization of the trabecular meshwork, the Tyvek® tray lid containing the iStent *inject* W system should be opened and presented to the user. The device should be handled in the sterile field. Caution: Do not use the device if the Tyvek lid has been opened or if the packaging appears damaged. In such cases, the sterility of the device may be compromised.
e. Hold the injector as shown in **Figure 5** with your index finger comfortably on the micro insertion sleeve retractor and within reach of the stent delivery button.

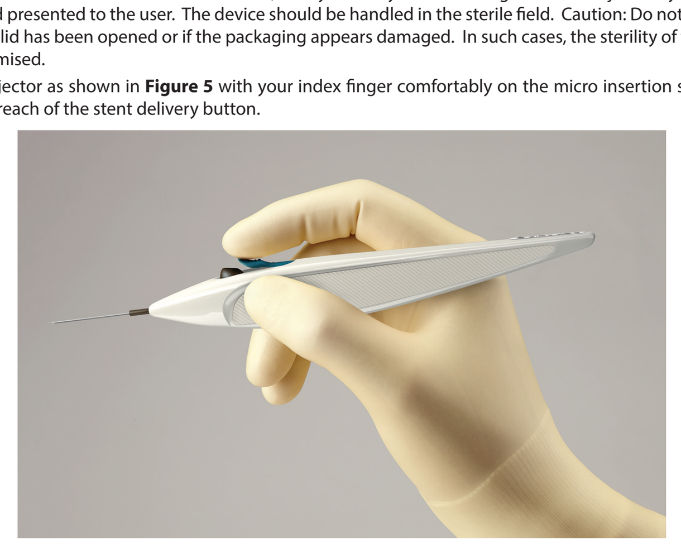

Figure 5. Hand position on injector

f. Injection of two stents:
   a. Inject cohesive viscoelastic into the anterior chamber to assist with chamber maintenance.
   b. Remove the Tube Protector prior to entering the eye.
   c. Place injector through the same temporal corneal incision used to perform cataract surgery, being careful to avoid contact with the cornea and iris in order to minimize sequelae associated with device-cornea touch, stent obstruction and/or iritis. Guide the injector across the anterior chamber, just beyond the pupillary margin, and then slide back the micro-insertion sleeve retractor (teal colored) to expose the micro insertion tube and trocar.

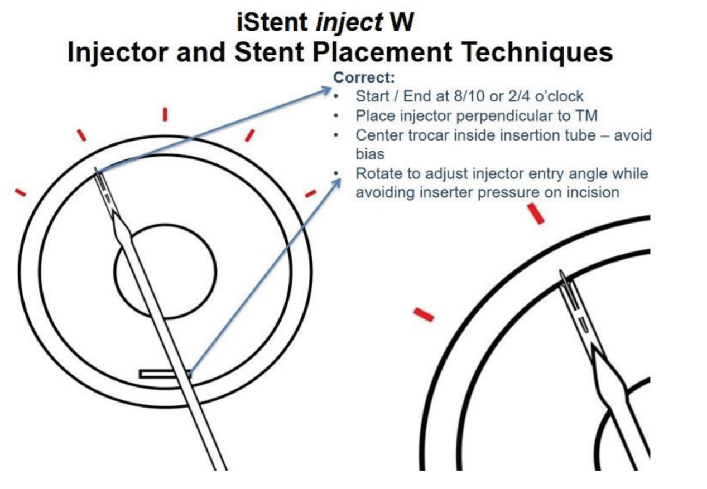

Figure 6. iStent *inject* W Implant Location

d. Locate the trabecular meshwork and select an implant location **(Figure 6)**. Apply light pressure (or Dimple) onto the trabecular meshwork with the injector to deliver the stent **(Figure 7)**.

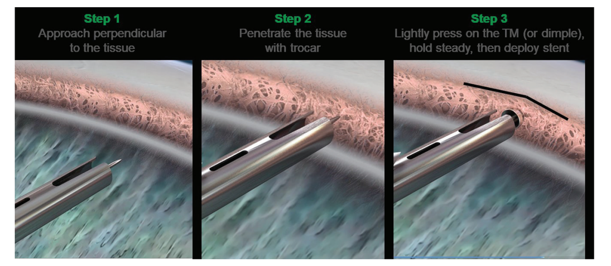

Figure 7. iStent *inject* W Implant Procedure (left: approach the TM; center: trocar pierces TM; right: dimple tissue and inject)

e. Center the trocar inside the micro-insertion tube, relax hand and squeeze the stent delivery button with your index finger. A single audible click will indicate that the first stent has been delivered from the injector through the trabecular meshwork and into Schlemm's Canal. Look through the micro-insertion tube window during stent implantation to verify the stent is securely in place within the tissue before withdrawing injector back.
f. Important: Hold the stent delivery button down and carefully withdraw the injector from the stent prior to releasing your finger from the stent delivery button.
g. Upon release of the stent delivery button, a second audible click will indicate that the next stent is in position and ready to deliver.
h. Carefully move the injector at least two clock hours away from the first stent implant. Approach the trabecular meshwork and repeat steps c - f.
i. After successful implantation of the second stent, carefully withdraw the injector from the implant site, release the stent delivery button and remove the injector from the eye.
j. Confirm proper placement of the two implanted stents, ensuring that each stent flange is visible in the anterior chamber (shown below in **Figure 8**).
k. Note: minimal blood reflux is a normal physiological response to placement of the stents, although this does not occur in all cases.

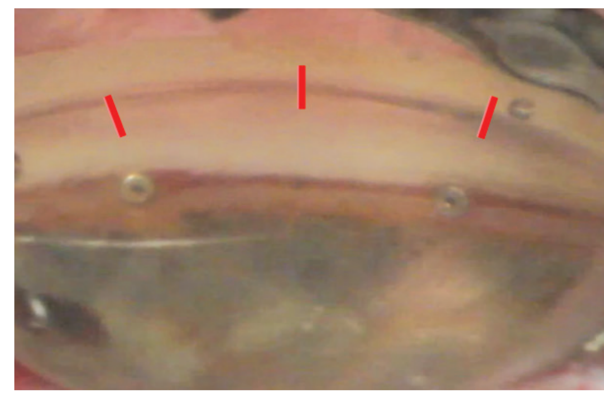

Figure 8. iStent *inject* W Implant Sites

Important Notes:

l. If the first stent is under implanted **and** remains on the trocar, then use an alternative "flush technique" procedure to re-attempt stent implantation in the nearest available trabecular meshwork tissue (within 1 clock hour away); **see Figure 9**.
m. If the first stent is under implanted **and does not** remain on trocar, this stent can be 'rethreaded' onto the trocar by placing the trocar through the central inlet **(Figure 9)**. Use the alternative "flush technique" to implant the stent.

Figure 9. iStent *inject* W rethreading of stent (top) and flush technique (bottom)

n. Re-loading can be considered if the surgeon prematurely releases a stent prior to engaging the trocar with the trabecular meshwork.
o. If there is only one stent remaining in the injector, it's important to use the standard "dimple technique" to implant the stent after it's been rethread onto the trocar.
p. There are a total of four positions available on the injector to implant the two stents. After the stent delivery button has been depressed for the fourth time, the injector will no longer function.
q. In the event that the first injector does not deliver two stents successfully, confirm that the number of stents implanted is less than two (2) before utilizing a second injector. Perform the following steps:
   - Inspect the micro-insertion tube under the surgical microscope and verify that at least one stent remains within the injector; or, verify that at least one stent has been retrieved from the eye.
   - To prevent implantation of more than two stents, do not attempt delivery of additional stents with a second injector above the number verified still within the first injector or retrieved from the eye.
r. At the end of the procedure, the following should be performed:
   - Irrigate the anterior chamber with balanced salt solution (BSS) through the corneal wound manually, or with automated irrigation/aspiration to remove viscoelastic and refluxed blood. Repeat as needed until all viscoelastic has been removed.
   - Inflate the anterior chamber with saline solution as needed to achieve physiologic pressure.
   - Ensure that the corneal incision is sealed, and place 10-0 nylon suture if needed.

Postoperative Instructions

1. Patients should be managed postoperatively for IOP increases that may occur in the early postoperative period as a possible sequelae following cataract surgery in patients with glaucoma. Additionally, monitor the patient postoperatively and consider an appropriate treatment regimen to reduce intraocular pressure if need be.
2. Gonioscopy should be performed to assess the iStent *inject* W position postoperatively.
3. Ultrasound biomicroscopy (UBM) is a useful adjunctive diagnostic aid in case of poor visualization of stents via gonioscopy.
4. Variations in gonioscopic visualization and limitations of UBM may prevent localization of a stent. However, in the absence of clinical sequelae, device adjustment or removal is not recommended.
5. It is highly recommended that Glaukos be contacted prior to post-operative device removal.

Postoperative Retrieval of an Implanted Stent

If the surgeon determines that an instrument is required to recapture a stent after the procedure, micro forceps of the surgeon's choice can be used by the surgeon as follows:

1. Prep the patient as one would for stent implantation surgery.
2. Re-open the eye at the preferred location in order to reach the stent. A clear corneal incision measuring approximately 1.5 mm in length is recommended.
3. Use cohesive viscoelastic to inflate the anterior chamber to create access to the stent's location, move the stent away from a delicate structure if loose, and/or protect intraocular tissues.
4. Use a gonioscope if needed to visualize the location of the stent in the anterior chamber.
5. Insert a micro forceps device through the corneal incision and grasp the stent in a convenient and secure manner before removing the stent from the anterior chamber.
6. Irrigate the anterior chamber with balanced salt solution (BSS) through the corneal wound to remove all viscoelastic. Press down on the posterior edge of the incision as needed to facilitate complete removal of viscoelastic. Repeat as needed until all viscoelastic has been removed.
7. Inflate the anterior chamber with saline solution as needed to achieve normal physiologic pressure.
8. Ensure that the corneal incision is sealed.

8. ADVERSE EVENT REPORTING

Adverse events and/or potentially sight-threatening complications that may reasonably be regarded as device related must be reported to Glaukos Corporation at:

U.S. Toll Free Phone Number: 1-800-GLAUKOS (452-8567)

Alternate Phone Number: 949-367-9600

Fax Number: 949-297-4540

9. HOW SUPPLIED

The iStent *inject* W Trabecular Micro-Bypass System is supplied as follows. Two stents are preloaded within the single-use injector system, and the system is provided sterile and non-pyrogenic in a Tyvek tray. Each stent system is individually serialized, and the serial number is provided on the tray lid and unit carton. The device has been sterilized by gamma radiation.

10. STORAGE REQUIREMENTS

The device should be stored at room temperature in the range of 15-30˚ C.

11. EXPIRATION DATE

The expiration date on the device package (Tyvek tray lid) is the sterility expiration date. In addition, there is a sterility expiration date that is clearly indicated on the outside of the unit carton. Sterility is assured if the tray seal is not punctured or damaged before the expiration date. This device should not be used past the indicated sterility expiration date.

12. RETURN GOODS POLICY

Please contact Glaukos Corporation.

13. iSTENT *INJECT*® G2-M-IS SYSTEM - PIVOTAL CLINICAL TRIAL RESULTS

The safety and effectiveness of the iStent *inject*® System was assessed through a clinical trial, known as the iStent *inject* Pivotal Trial (Protocol GC-008) under Investigational Device Exemption (IDE) G100326[1]. The aim of the iStent *inject* Pivotal Trial was 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 (OAG). Data from this clinical study were the primary basis for the PMA approval decision. Key safety and effectiveness information derived from the pivotal study are summarized below.

[1]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 components and to the manufacturing process to improve manufacturability and to accommodate production scale-up. Validation testing was performed to demonstrate that injector functionality was not altered. Clinical testing is not available for the modified injector.

A. Study Design

The iStent *inject* Pivotal Trial (Protocol GC-008) 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* 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 ≥ 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* and 94 control) for the first set of hypotheses, and 274 iStent *inject* eyes for the second set of hypotheses. For safety, a sample size of 300 iStent *inject* 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* eyes and 123 control eyes were to be randomized. Therefore, the sample size was set at 500 randomized eyes (375 iStent *inject* 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 subjects 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 1** below
  - maximum coefficient of variation (CV) = 0.45

Table 1. Minimum Endothelial Cell Density at Screening

Age at time of enrollment	Minimum endothelial cell density
45 years	2200 cells/mm2
46 to 55 years	2000 cells/mm2
56 to 65 years	1800 cells/mm2
> 65 years	1600 cells/mm2

- Subjects 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.

Subjects 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 SLT within 90 days prior to screening
- prior 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 subjects were scheduled to return for follow-up examinations at defined intervals through 24 months. **Table 2** shows the schedule of events and procedures at each protocol-required visit.

Table 2. 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. Clinical Endpoints

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.

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.

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.

B. Accountability of PMA Cohort

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 = 358) 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%) were discontinued due to cataract surgery-related complications rendering them ineligible for study randomization. The remaining 58.2% (n = 505) 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 and preoperative characteristics of the study population were as follows:

Table 3. 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 4. 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 5**). 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 386 eyes that were implanted with stents, 380 eyes (98.2%) were implanted with 2 stents. Four eyes (1.0%) were implanted with 3 stents and 2 eyes (<1%) were implanted with 1 stent.

In most eyes (85.5%; n = 331), 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 = 315). No associated clinical sequelae were noted in any cases in which stent implantation difficulty was reported.

Table 5
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 x 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

All safety analyses were performed on the Safety population. Findings are summarized for events occurring during the intraoperative period through the 24-month post-operative visit. The key safety outcomes for this study are presented below in **Tables 6 to 8**.

Best Spectacle Corrected Visual Acuity (BSCVA)

Most eyes in both groups achieved 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%) than in the control group (98.2%).

Adverse Effects that Occurred in the PMA Clinical Study

Intraoperative AEs

A summary of intraoperative AEs is shown in **Table 6.** 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 6. 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 x 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 = 209] in the iStent *inject* group and 62.2% of subjects [n = 74] 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 7**. Anterior segment inflammation, which was generally mild, was reported in 5.7% of iStent *inject* subjects and 4.2% of Control subjects.

Table 7. 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 14	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 x 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 7**, 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%) 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%) 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%) each of peripapillary atrophy, retinal flap tears, retinal hole and notching; 4 cases (1.0%) of deep stents and transient mild ocular discomfort; 5 cases (1.3%) of subconjunctival hemorrhage and 7 cases (1.8%) of goniosynechiae. AEs that occurred at < 2% in the control group included 1 case (0.8%) each of anterior scleritis, central retinal artery occlusion, corneal ulcer, flashes, iris neovascularization and IOL dislocation; and 2 cases (1.7%) 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=3) in the iStent *inject* group and 2.5% (n=3) in the control group. iStent *inject* 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%) were determined to be device related including all cases of stent obstruction, deep stents, 3 stents implanted, 1 stent implanted, 2 stents 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%) of intraocular inflammation, 7 cases (1.8%) of goniosynechiae, 3 cases (0.8%) of intraoperative corneal abrasion, and 1 case (0.3%) each of iris strand and ocular irritation.

[2]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.

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 = 21) and 5.0% (n = 6) of subjects in the control group. Secondary surgeries reported in both groups are shown in **Table 8**.

Table 8. 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 x 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 Operative/Postoperative Observations

Reporting of other ocular observations was at the study investigator's discretion. Similar data may not be reported for every subject, or consistently within the course of a given subject'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 = 14). 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 = 30); microhyphema (3.9%; n = 15); 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 = 10) eyes in the iStent *inject* group and 5.0% (n = 6) 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% in the iStent inject group and 9.5% in the control group) experienced ECL > 30% at 24 months postoperatively.

2. Effectiveness Results

Results from the primary and secondary endpoints are shown in **Table 9**. 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 9. 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[1]
Medication-free mean DIOP (mmHg) change from baseline[1]	-7.0	-5.4		< 0.001[1]

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 and 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 10**.

Table 10. 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 x 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 surgeries include:
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. Summary of Supplemental Clinical Information

A. For the pivotal trial of the iStent inject, the Ocular Surface Disease Index (OSDI®) was self-administered by study subjects. The OSDI questionnaire contains 12 questions involving ocular symptoms, vision-related function and environmental triggers experienced by the subject during the past week, and is assessed on a scale of 0 to 100 with higher scores representing greater disability. **Table 11** 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). 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 the **Table 11**.

Table 11
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	20.20	21.65	22.63	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 OSDI.

1. 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.

B. In the iStent inject pivotal trial, at 24 months, the proportion of subjects with medication-free diurnal IOP ≤ 18 mmHg was 63.2% in the treatment group and 50.0% in the control group (difference 13.2%; 95% CI 2.9%, 23.4%).[1]

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

D. Of the subjects 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.

[a]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).

14. POST-APPROVAL STUDY RESULTS

iStent inject Extended Follow-up of Pivotal Study Cohort (Protocol # IG2M-104-CONT)

Study Objective

In accordance with the PMA conditions of approval, extended follow-up of the pivotal study (GC-008) cohort was conducted. The IG2M-104-CONT protocol was approved by FDA April 16, 2019, and the updated protocol was approved by the FDA on April 30, 2020. The goal of the post-approval study was to evaluate the long-term rate of clinically relevant complications associated with iStent inject placement and stability.

Study Design

In this long-term safety, multicenter, observational post-approval study with no planned interventions study, subjects who were enrolled and randomized in the pivotal study were eligible for enrollment.

Study Population/Data Source

In the iStent inject pivotal study, a total of 505 subjects with mild to moderate primary open-angle glaucoma were randomized in a 3:1 fashion to implantation of the iStent inject after uncomplicated cataract surgery (iStent inject group, n=387) or to cataract surgery only (control group, n=118). Subjects were asked to consent for long-term follow of 60 months post-randomization.

Study Endpoint

The primary endpoint was the rate of clinically relevant complications associated with iStent inject placement and stability as determined at 60 months, specifically, the rate of sight-threatening adverse events and secondary surgical intervention to modify device position.

Total Number of Enrolled Study Sites and Subjects

A total of 24 sites of the 40 sites that randomized subjects into pivotal study agreed to participate in the post-approval study. Of the total of 505 subjects randomized in the pivotal study, 227 subjects (178 iStent inject subjects and 49 control subjects) reconsented to participate in the post-approval study.

Study Visits and Length of Follow-Up

The protocol specified a follow-up visit at 48 and 60 months to collect additional safety data. Due to the delay in the approval of the post-approval study protocol, all eligible subjects were beyond the Month 48 visit window. Therefore, data was collected at Month 60 visits. The mean follow-up from surgery to final visit was 2271.6 (SD 335.6) days in iStent inject group, and 2291.0 (SD 323.7) days in the control group.

Final Safety Findings – Sight-Threatening Adverse Events

Table 12 presents all postoperative sight-threatening adverse events reported in the study eye in the pivotal study and post-approval study by time period. A lower proportion of subjects in the iStent inject group experienced sight-threatening adverse events than the control group at each time period (i.e., 16.8% vs. 20.2% through Month 24; 3.6% vs. 7.3% between Month 24 and Month 36; 15.7% vs. 36.7% between Month 36 and Month 60).

Other BSCVA-Related Adverse Events

The proportion of subjects with BSCVA loss 2 lines or more at or after 3 months postoperative was low, specifically, 0.3% in the iStent inject group (n=1) and 0.8% in the control group (n=1). As described in the original PMA report:

- The iStent inject subject was reported with glaucoma progression characterized by visual field loss at the Month 18 visit and underwent trabeculectomy and Express shunt implantation. At the Month 24 visit, diurnal IOP was 8.3 mmHg on 1 medication and BSCVA was 20/66.
- BSCVA for the control subject fluctuated and was 20/26 at baseline, 20/83 at Month 3, 20/36 at Month 12, and 20/50 at Month 24.

Three AE categories involving BSCVA loss vs. best recorded BSCVA at any postoperative visits were used:

- The proportion of subjects with BSCVA loss 2 lines or more and less than 3 lines at Month 60 vs. best recorded BSCVA at any postoperative was 6.2% in the iStent inject group and 3.4% the control group. In all eyes, BSCVA at the Month 60 visit was 20/36 or better.
- The proportion of subjects with BSCVA loss 3 lines or more at study exit vs. best recorded BSCVA at any postoperative visit and 20/40 or better was 0.8% in the iStent inject group and 1.7% the control group.
- The proportion of subjects with BSCVA loss 3 lines or more at study exit vs. best recorded BSCVA at any postoperative visit and 20/40 or worse was 0.8% in the iStent inject group and 1.7% the control group. These AEs were not considered device-related. A brief description for each subject is provided below:
  - The first iStent inject subject had BSCVA of 20/46 at the Month 60 visit. BSCVA fluctuated throughout the study in this 93 year-old subject, and the site considered the variation in vision to be normal and attributed to tear film quality and quantity and possibly due to slight epiretinal membrane.
  - The second iStent inject subject had BSCVA of 20/115 at the Month 36 visit due to PCO.
  - The third iStent inject subject experienced retinal detachment at approximately 40 months postoperative and that resolved following laser retinopexy; BSCVA was 20/46 at the Month 60 visit.
  - The first control subject underwent XEN stent implantation approximately 62 months postoperative; BSCVA was 20/63 at the Month 60 visit that occurred 4 months after the XEN implantation.
  - The second control subject had BSCVA of 20/1002 at Day 175 which persisted through the Month 36 visit and decreased to hand motions at the Month 60 exam. The profound loss in BSCVA at Day 175 (vs. Month 1 postoperative BSCVA of 20/16) coincided with central retinal artery occlusion.

Table 12
Postoperative Sight-Threatening Adverse Events in the Study Eye
(Data from GC-008 and IG2M-104-CONT Study)

	Cataract Surgery with iStent inject					
	GC-008 Data Through Month 24 N = 386		GC-008 Between Month 24 and Month 36 N = 138		IG2M-104-CONT Between Month 36 and Month 60 N = 178	
Sight Threatening Adverse Event	n of Subjects with Event (%)	n of Events	n of Subjects with Event (%)	n of Events	n of Subjects with Event (%)	n of Event
Total	**65 (16.8%)**	**90**	**5 (3.6%)**	**5**	**28 (15.7%)**	**37**
Age-related macular degeneration	2 (0.5%)	2	1 (0.7%)	1	5 (2.8%)	5
BSCVA loss 3 lines or more at study exit vs. best recorded BSCVA at any postoper-ative visit and worse than 20/40	0	0	1 (0.7%)	1	1 (0.6%)	1
Branch retinal vein occlusion	1 (0.3%)	1	0	0	0	0
Central retinal artery occlusion	0	0	0	0	0	0
Central retinal vein occlusion	0	0	0	0	0	0
Clinically significant cystoid macular edema	5 (1.3%)	5	0	0	0	0
Corneal edema >= 30 days	1 (0.3%)	1	0	0	0	0
Corneal opacity	4 (1.0%)	4	0	0	0	0
Corneal striae	1 (0.3%)	1	0	0	0	0
Corneal ulcer	0	0	0	0	0	0
Cystoid macular edema	2 (0.5%)	2	0	0	0	0
Disc hemorrhage	4 (1.0%)	4	0	0	0	0
Epiretinal membrane	9 (2.3%)	9	0	0	3 (1.7%)	3
Glaucoma progression requiring surgical intervention	4 (1.0%)	4	1 (0.7%)	1	4 (2.2%)	6
IOL dislocation	0	0	0	0	0	0
IOP increase >= 10 mmHg vs. baseline IOP occurring at >= Month 1	8 (2.1%)	9	0	0	0	0
IOP increase requiring management with oral or intravenous medications or with surgical intervention at >= Day 1 to Week 1	2 (0.5%)	2	0	0	0	0
IOP increase requiring management with oral or intravenous medications or with surgical intervention at > Week 1 to < Month 1	2 (0.5%)	2	0	0	0	0
IOP increase requiring management with oral or intravenous medications or with surgical intervention at >= Month 1	1 (0.3%)	1	2 (1.4%)	2	10 (5.6%)	10
IOP increase requiring management with oral or intravenous medications or with surgical intervention at Day 0 (6 hours) to Day 1	2 (0.5%)	2	0	0	0	0
IOP not at target requiring surgical intervention	0	0	0	0	5 (2.8%)	6
Increase in C/D ratio > 0.3	0	0	0	0	1 (0.6%)	1
Iris atrophy	1 (0.3%)	1	0	0	0	0
Ischemic Optic Neuropathy	0	0	0	0	0	0
Medication intolerance requiring surgical intervention	3 (0.8%)	3	0	0	0	0
Segmental loss of neuroretinal rim (notching)	3 (0.8%)	3	0	0	0	0
Vitreous hemorrhage	0	0	0	0	0	0
Worsening glaucoma	0	0	0	0	0	0
	Cataract Surgery Only					
	GC-008 Data Through Month 24 N=119		GC-008 Between Month 24 and Month 36 N=41		IG2M-104-CONT Between Month 36 and Month 60 N=49	
Sight Threatening Adverse Event	n of Subjects with Event (%)	n of Events	n of Subjects with Event (%)	n of Events	n of Subjects with Event (%)	n of Events
Total	**24 (20.2%)**	**39**	**3 (7.3%)**	**3**	**18 (36.7%)**	**26**
Age-related macular degeneration	2 (1.7%)	2	0	0	1 (2.0%)	1
BSCVA loss 3 lines or more at study exit vs. best recorded BSCVA at any postoper-ative visit and worse than 20/40	1 (0.8%)	1	0	0	1 (2.0%)	1
Branch retinal vein occlusion	0	0	0	0	0	0
Central retinal artery occlusion	0	0	0	0	0	0
Central retinal vein occlusion	0	0	0	0	0	0
Clinically significant cystoid macular edema	2 (1.7%)	2	0	0	0	0
Corneal edema >= 30 days	0	0	0	0	0	0
Corneal opacity	3 (2.5%)	3	0	0	0	0
Corneal striae	0	0	0	0	0	0
Cystoid macular edema	1 (0.8%)	1	0	0	1 (2.0%)	1
Disc hemorrhage	1 (0.8%)	2	0	0	2 (4.1%)	2
Epiretinal membrane	3 (2.5%)	3	1 (2.4%)	1	0	0
Glaucoma progression requiring surgical intervention	1 (0.8%)	1	0	0	1 (2.0%)	1
IOL dislocation	1 (0.8%)	1	0	0	0	0
IOP increase >= 10 mmHg vs. baseline IOP occurring at >= Month 1	1 (0.8%)	1	0	0	0	0
IOP increase requiring management with oral or intravenous medications or with surgical intervention at >= Day 1 to Week 1	1 (0.8%)	1	0	0	0	0
IOP increase requiring management with oral or intravenous medications or with surgical intervention at > Week 1 to < Month 1	0	0	0	0	0	0
IOP increase requiring management with oral or intravenous medications or with surgical intervention at >= Month 1	4 (3.4%)	4	0	0	0	0
IOP not at target requiring surgical intervention	0	0	0	0	0	0
Increase in C/D ratio > 0.3	0	0	0	0	2 (4.1%)	2
Iris atrophy	0	0	0	0	0	0
Ischemic Optic Neuropathy	0	0	0	0	1 (2.0%)	1
Medication intolerance requiring surgical intervention	0	0	0	0	6 (12.2%)	6
Nerve fiber layer loss	2 (1.7%)	2	0	0	0	0
Non-proliferative diabetic retinopathy	3 (2.5%)	3	0	0	0	0
Optic nerve thinning/cupping	1 (0.8%)	1	0	0	0	0
Peripapillary atrophy	0	0	0	0	0	0
Posterior vitreolysis	0	0	0	0	0	0
Retinal detachment	0	0	0	0	0	0
Retinal dissues	0	0	0	0	0	0
Retinal flap tears	0	0	0	0	0	0
Retinal hemorrhage	0	0	0	0	0	0
Retinal hole	0	0	0	0	0	0
Retinal pigment epithelial changes	0	0	0	0	0	0
Retinal tear	0	0	0	0	0	0
Segmental loss of neuroretinal rim (notching)	0	0	0	0	0	0
Visual field loss >= 2.5 dB	1 (0.8%)	1	1 (2.4%)	1	1 (2.0%)	1
Vitreous hemorrhage	1 (0.8%)	1	0	0	0	0
Worsening glaucoma	0	0	0	0	0	0

As per the 2018 FDA conditions of approval, BSCVA loss ≥ 3 lines compared to best recorded BSCVA at any postoperative visit[a] was defined as a sight-threatening adverse event. In 2021, the term "BSCVA loss 3 lines or more at study exit vs. best recorded BSCVA at any postoperative visit and worse than 20/40" was a sight-threatening adverse event, and "BSCVA loss 3 lines or more at study exit vs. best recorded BSCVA at any postoperative visit and 20/40 or better" was not considered a sight-threatening adverse event by the Chief Medical Office; however, this information is provided in the paragraph above. The proportion of subjects with BSCVA loss 3 lines or more at study exit vs. best recorded BSCVA at any postoperative visit and 20/40 or better was 0.8% in the iStent inject group and 1.7% the control group.

Secondary Surgical Interventions

Table 13 presents all secondary ocular surgeries, some of which were to achieve further IOP reduction, reported in the pivotal study and post-approval study by time period. A similar proportion of subjects in the iStent inject group and the control group experienced secondary ocular surgeries through Month 36 (i.e., 5.4% vs. 5.0% through Month 24; 2.9% vs. 2.4% between Month 24 and Month 36); and a lower proportion of subjects in the iStent inject group experienced secondary ocular surgeries between Month 36 and Month 60 than the control group (12.9% vs. 28.6%). There were no device repositionings or device explants.

One subject with an SSI of laser for stent obstruction had reported with an adverse event of IOP increase approximately 5 years postoperative and underwent Nd:YAG laser for stent obstruction the same day to rule out stent obstruction, per the PI. The subject ultimately underwent implantation of a XEN stent to address the elevated IOP at which point the AE of elevated IOP resolved.

Table 13
Secondary Surgical Interventions in the Study Eye
(Data from GC-008 and IG2M-104-CONT Study)

	GC-008 Data Through Month 24 N = 386		GC-008 Between Month 24 and Month 36 N = 138		IG2M-104-CONT Between Month 36 and Month 60 N = 178	
Procedure Term	n of Subjects with Event (%)	n of Events	n of Subjects with Event (%)	n of Events	n of Subjects with Event (%)	n of Event
	Cataract Surgery with iStent inject					
Canaloplasty (aborted)	0	0	0	0	1 (0.6%)	1
Canaloplasty (completed)	0	0	0	0	2 (1.1%)	2
IOL exchange	1 (0.3%)	1	0	0	0	0
IOL repositioning	0	0	0	0	0	0
Laser for stent obstruction	3 (0.8%)	3	0	0	1 (0.6%)	1
Laser retinopexy	6 (1.6%)	7	0	0	2 (1.1%)	2
Micropulse diode laser trabeculoplasty	0	0	0	0	2 (1.1%)	3
Parenteral phaboxgulation	0	0	0	0	0	0
Posterior vitreolysis	2 (0.5%)	2	0	0	0	0
Removal of residual cortex	1 (0.3%)	1	0	0	0	0
Selective laser trabeculo-plasty	2 (0.5%)	2	3 (2.2%)	3	15 (8.4%)	17
Trabeculectomy with/without Express shunt	4 (1.0%)	4	1 (0.7%)	1	2 (1.1%)	2
Vitrectomy	1 (0.3%)	1	0	0	1 (0.6%)	1
Vitrectomy with membrane peel	1 (0.3%)	1	0	0	0	0
XEN stent	0	0	0	0	3 (1.7%)	3
iStent	0	0	0	0	0	0
Total	**21 (5.4%)**	**22**	**4 (2.9%)**	**4**	**23 (12.9%)**	**30**
	Cataract Surgery with iStent inject					
Canaloplasty (aborted)	0	0	0	0	0	0
Canaloplasty (completed)	0	0	0	0	1 (2.0%)	1
IOL exchange	0	0	0	0	0	0
IOL repositioning	1 (0.8%)	1	0	0	0	0
Laser for stent obstruction	0	0	0	0	0	0
Laser retinopexy	0	0	0	0	0	0
Micropulse diode laser tra-beculoplasty	0	0	0	0	0	0
Parenteral phaboxgulation	1 (0.8%)	1	0	0	1 (2.0%)	1
Posterior vitreolysis	0	0	0	0	0	0
Removal of residual cortex	0	0	0	0	0	0
Selective laser trabeculo-plasty	3 (2.5%)	3	1 (2.4%)	1	10 (20.4%)	11
Trabeculectomy with/without Express shunt	1 (0.8%)	1	0	0	1 (2.0%)	1
Vitrectomy	0	0	0	0	0	0
Vitrectomy with membrane peel	1 (0.8%)	1	0	0	0	0
XEN stent	0	0	0	0	1 (2.0%)	1
iStent	0	0	0	0	1 (2.0%)	1
Total	**6 (5.0%)**	**7**	**1 (2.4%)**	**1**	**14 (28.6%)**	**16**

Study Strength and Weaknesses

The mean percent change in ECD from baseline to Month 60 was -14.3% (SD 13.4; range -68.0% to +33.8%) for the iStent inject group and -14.8% (SD 10.3%; range -37.8% to +9.1%) for the control group. The mean percent change in ECD was similar in the treatment and control groups.

The percentage of eyes with an ECL > 30% at the Month 60 visit was 9.4% in the iStent inject group (n=16) and 6.3% in the control group (n=3).

The percentage of eyes with an ECD of < 1000 cells/mm2 at the Month 60 visit was 1.2% in the iStent inject group (n=2) and 0% in the control group.

Note, two eyes (1.2%) in the iStent inject group reported with both ECL > 30% and ECD < 1000 cells/mm2 at the Month 60 visit. Both these subjects were from the same site, specifically:

- The first subject was 87 years old at the time of the Month 60 visit that was conducted 6.5 years after iStent inject implantation and underwent SLT 3.3 years following iStent inject implantation.
- The other subject was diabetic, and ECL followed trabeculectomy with Express shunt implantation performed 4.7 years following iStent inject implantation.

Stent Visibility

With the exception of one subject, all implanted stents were visualized in all subjects. In one subject with 2 implanted stents not visualized via gonioscopy, the implant locations of the stents were 2:30 and 3:30; both stents were visible at every visit through the Month 24 visit, and the subject declined to attend the Month 36 visit. The PI was not able to visualize stents via gonioscopy at Month 60. Ultrasound biomicroscopy (UBM) was not performed due to COVID-19 (unavailability of subject and of UBM technician). No AEs were reported at the Month 60 visit.

Study Strength and Weaknesses

The original study design was a prospective, randomized, concurrently controlled, parallel group, multicenter study; in this study, subjects consented to be followed for 24 months postoperative. Subsequently, a subset of subjects consented to an additional follow-up visit at 36 months postoperative. Subjects had to reconsent to be assessed at the Month 48 and Month 60 visit. Due to the delay in the approval of the post-approval study protocol, all eligible subjects were beyond the Month 48 visit window, and only Month 60 visits were conducted. Enrollment was hampered by the COVID-19 pandemic which resulted in sites and individual subjects declining to participate in this post-approval study. A lower proportion of subjects in the iStent inject group experienced post-operative sight-threatening adverse events and underwent secondary surgical intervention than in the control group Importantly, there were no UADEs identified during the study, which extended to 5 years after iStent inject implantation + cataract surgery.

15. LABELING

Not all symbols may be included in the labeling of this product.

Symbol	Definition	Symbol	Definition
REF	Catalogue/Model Number		Consult instructions For use
SN	Serial Number (for the stent)		Manufacturer
LOT	Lot Number	STERILE R	Sterilized by Gamma Irradiation
	Do not reuse	Rx Only	For prescription use only
yyyy-mm-dd	Use-by date (year-month-day)	5°C 25°C	Temperature Storage Requirement
	Do not use if package is damaged		MR Conditional

16. MRI SAFETY INFORMATION

Non-clinical testing has demonstrated that the iStent inject W Trabecular Micro-Bypass System Model G2-W is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 3 T 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 4 W/kg

Under the scan conditions defined above, the iStent inject W Trabecular Micro-Bypass System Model G2-W 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.

17. CAUTION

Federal law restricts this device to sale by, or on the order of, a physician.

Physician training by certified Glaukos personnel is required prior to use of this device. Training consists of three main parts:

- Didactic session
- Simulated implantation of iStent inject W
- Supervised iStent inject W implantation of clinical cases until implantation proficiency is demonstrated

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