

DIRECTIONS FOR USE/PACKAGE INSERT
Glaukos® Corporation iStent inject® Trabecular Micro-Bypass System

DIRECTIONS FOR USE TABLE OF CONTENTS

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1. DEVICE DESCRIPTION

The iStent inject® Trabecular Micro-Bypass System Model G2-M-IS contains two preloaded intraocular stents that are manufactured from titanium (Ti6Al4V ELI) and are coated with stearalkonium heparin (note: the heparin is from a porcine source). The stent has a single piece design, is 230 µm in diameter, 360 µm in height, and the central inlet and outlet lumen has a diameter of 80 µm (Figure 1). The head of the stent has four side outlets that each have a diameter of 50 µm.



Figure 1. iStent inject® Stent Dimensions

The iStent inject 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).

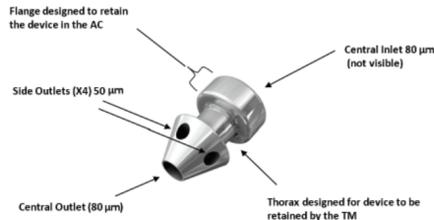


Figure 2. iStent inject Model GTS400 Design

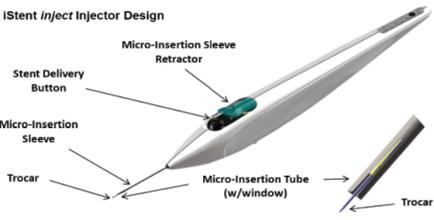


Figure 3a. iStent inject G2-M-IS Injector Design

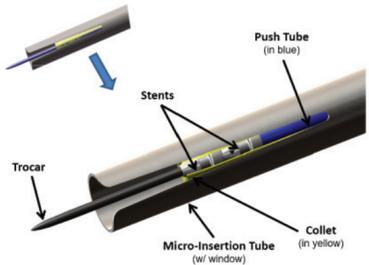


Figure 3b. iStent inject G2-M-IS Injector Distal End

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

2. INDICATIONS FOR USE

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

3. CONTRAINDICATIONS

The iStent inject Trabecular Micro-Bypass System Model G2-M-IS 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 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 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 stent implanted in their eye.
2. After the surgery, the surgeon should give the patient the Patient ID card (enclosed in the iStent inject 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 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 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 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 cilioablate 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.

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, iridodiolysis, 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.
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 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 gonioscopium to ensure that a good view is available at the nasal implant location.
- c. Place the gonioscopium on the cornea and position the patient and surgical microscope as needed to visualize the trabecular meshwork, through the gonioscopium, 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 Implant Site



Figure 4b. iStent inject Implant Site

- d. After visualization of the trabecular meshwork, the Tyvek® tray lid containing the iStent inject 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. 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.

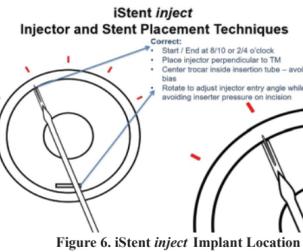


Figure 6. iStent inject Implant Location

- 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® 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 5c-5f.
- 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 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 site (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.

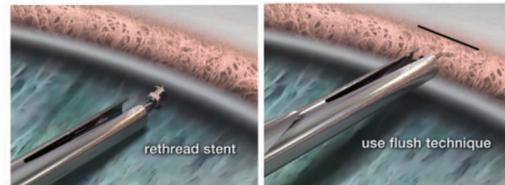


Figure 9. iStent inject rethreading of stent (left) and flush technique (right)

- 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 rethreaded 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 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 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. 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. 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.

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 $\geq 20\%$ reduction in medication-free diurnal IOP at Month 24. The first hypothesis was that a larger proportion of eyes who received the iStent inject would meet the primary effectiveness endpoint than those who received cataract surgery alone. The second hypothesis was that the 24-month IOP response rate of the iStent inject group would be better than 50%. This hypothesis was to be tested if the observed Cataract surgery-only response rate was greater than 35%.

The sample size calculation was based on the hypothesis testing for effectiveness, and evaluation for safety. For effectiveness, the sample size was estimated to be at least 376 eyes (282 iStent inject 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).

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.

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 $\geq 20/40$ or worse with medium Brightness Acuity Meter (BAM)
- 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/mm ²
46 to 55 years	2000 cells/mm ²
56 to 65 years	1800 cells/mm ²
> 65 years	1600 cells/mm ²

- 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-approved 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
- traumatic/iridial 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	1 Day	Day 1	Week 1	Month 1	Month 2	Month 3	Month 4	Month 6	Month 12	Month 18	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												
Best Corrected VA (baseline) with BAM	X													
Best Spectacle Corrected VA (GTDERS)		X												
Pachymetry					X	X	X	X	X	X	X	X	X	X
Slit Lamp Exam					X	X	X	X	X	X	X	X	X	X
Specular Microscopy														
IOP via Application Tonometry	X				X	X	X	X	X	X	X	X	X	X
Diurnal IOP via Application Tonometry		X												
Gonioscopy (all subjects)	X	X			X	X	X	X	X	X	X	X	X	X
Ultrasound Biomicroscopy (UBM) Imaging					X	X	X	X	X	X	X	X	X	X
Diurnal Fundus Exam		X												
Central Assessment of Nerve Abnormality		X												

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:

Parameter	Cataract Surgery with iStent <i>inject</i> ¹		Cataract Surgery Only		Total N = 505
	N = 387	N = 118	N = 387	N = 118	
Age (Years)	Mean 69.0	70.1	69.2	70.1	69.2
	Standard Deviation 8.2	7.7	8.1	7.9	8.1
	Median 69	71	70	70	70
	Minimum 45	46	45	46	45
	Maximum 98	86	98	98	98
	P-value ²	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	0.439			
Race ³	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	0.21			
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

Parameter	Cataract Surgery with iStent <i>inject</i> ¹		Cataract Surgery Only		Total N = 505
	N = 387	N = 118	N = 387	N = 118	
Number of Ocular Hypotensive Medications at Screening	Mean 1	1	1	1	1
	Standard Deviation 1	1	1	1	1
	Median 1	1	1	1	1
	Minimum 0	0	0	0	0
	Maximum 4	4	4	4	4
	P-value ²	0.943			
Visual Field	Mean -3.92	-3.57	-3.84		
	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	2.94	3.12		
	P-value ²	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	545.5	546.0		
	Minimum 458.0	448.0	448.0		
	Maximum 620.0	620.0	620.0		
	P-value ²	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 ²	0.997			
Unmedicated IOP at Baseline (mmHg)	Mean 24.83	24.50	24.75		
	Standard Deviation 3.24	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 ²	0.328			
BCSCVA 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 ²	0.901			
Shaffer Angle Grade at Screening	III (25 - 35) 142/387 (36.7%)	40/118 (33.9%)	182/505 (36.0%)		
	IV (35 - 55) 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 ²		
Yes	71	18.3%
No	315	81.4%
NA	1	0.3%

Percent = Number ÷ N × 100%. The iStent *inject* was not attempted for a subject due to coughing fit after randomization.

¹ Reports of use of a second injector and of stent implantation difficulty are not mutually exclusive. Further, the same reason could be reported for 1 eye in both categories. The most common/notable reasons for use of a second injector include first injector did not deploy 2 stents (5.4%; n = 21); stent not adequately seated in trabecular meshwork (TM) (5.2%; n = 20); poor visibility (1.3%; n = 5); stent dislodged during I/A (0.3%; n = 1). The most common/notable reasons for stent implantation difficulty include injector did not deploy stent (5.9%; n = 23); stent not adequately seated in TM (6.2%; n = 24); injector initially did not (but did eventually) deploy stent (2.1%; n = 8); poor visibility (1.6%; n = 6); 2 stents implanted in same location (0.3%; n = 1). In these reports of 2nd injector used and/or stent implantation difficulty, no associated clinical sequelae were noted in any cases.

D. Safety and Effectiveness Results

1. Safety Results

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-ataract 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 stent. 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 <i>inject</i> ¹	Cataract Surgery Only ²	Difference in % 95% CI ³
Intraoperative adverse events during cataract surgery	1 Reports from 1 subjects	0 Reports from 0 subjects	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%)
Capitolhexia 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	1 (0.3%)	0 (0.0%)	0.3% (-0.2%, 0.8%)
Corneal abrasion	1 (0.3%)	0 (0.0%)	0.3% (-0.2%, 0.8%)
Intraoperative adverse events during iStent <i>inject</i> implantation	11 Reports from 11 subjects	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	2 (0.5%)		
1 stent implanted	1 (0.3%)		
2 stents implanted in same location	1 (0.3%)		
3 stents implanted	1 (0.3%)		
Corneal abrasion	3 (0.8%)		
Stent implanted in ciliary body	1 (0.3%)		

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

Postoperative AEs

There were no unanticipated adverse events. There were no reports of flat AC with lens cornea touch, shallow AC with iridoc traumatic orneal 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 <i>inject</i> ¹	Cataract Surgery Only ²	Difference in % 95% CI ³
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 ⁴	24 (6.2%)	NA	
Any intraocular inflammation (non pre-existing) remaining or arising after the protocol's specified medication regimen is completed ⁵	22 (5.7%)	5 (4.2%)	1.5% (-2.8%, 5.8%)
Secondary surgical intervention ⁶	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 postoperatively ⁷	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%)
Extracocular inflammation	9 (2.3%)	2 (1.7%)	0.7% (-2.1%, 3.4%)
Epiretinal membrane	9 (2.3%)	2 (1.7%)	0.7% (-2.1%, 3.4%)
IOP increase ≥ 10 mmHg vs. baseline IOP occurring at ≥ Month 1 ⁸	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 edema	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%)
Hypertension	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 ⁹	1 (0.3%)	3 (2.5%)	-2.3% (-5.1%, 0.6%)

The counts (n) are the number of subjects reported with the corresponding events. % = n ÷ N × 100%. There were no cases of iridodiolysis and no cases of significant vitreitis (<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. Seven 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