FDA Executive Summary

Prepared for the
July 30, 2010 meeting of the
Ophthalmic Devices Panel

P080030
Glaukos, Inc.
iStent Trabecular Micro-Bypass Stent
Model GTS-100 R/L

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1 Introduction

The information in this document comprises FDA's executive summary of premarket approval (PMA) application P080030 from Glaukos Corporation. Included is a description of the device, pre-clinical testing information, an overview of the pivotal clinical investigation conducted by Glaukos Corporation with respect to the clinical study protocol as well as the endpoints, results and statistical analyses, additional supportive data collected inside and outside United States (OUS) studies, and the proposed post-approval study protocol.

Pursuant to 21 CFR 814.20(e), the data contained in this summary includes updated adverse events as reported by the applicant in May, 2010.

Glaucoma devices are classified into both Class II and Class III devices, distinguished by the indications for use (IFU). Specifically, Class II devices are indicated for end-stage (refractory) glaucoma when other treatment options have failed, such as medications and filtering surgery. Class III devices are indicated for non end-stage (non-refractory) glaucoma, to be used before all other treatment options have been exhausted.

All implantable glaucoma devices currently on the U.S. market are Class II devices with exception to the Staar Aquaflow collagen glaucoma implant, which is PMA approved for "the maintenance of a sub-scleral space following non-penetrating deep sclerectomy used to facilitate aqueous outflow for the reduction of intraocular pressure in patients with open angle glaucoma where intraocular pressure remains uncontrolled while on maximally tolerated medical therapy. Therefore, this is the first PMA for a shunt-type device that is indicated for non-refractory glaucoma.

2 Device Description

The device (Figure 1) is designed to increase aqueous outflow by shunting aqueous humor from the anterior chamber to Schlemm's canal, bypassing the trabecular meshwork; thus, no filtering bleb is formed. The device is implanted into Schlemm's canal through the nasal trabecular meshwork using an "ab-interno," or intraocular method, immediately following successful cataract extraction and intraocular lens implantation. It is inserted into the anterior chamber through the cataract surgery incision.

The GTS100R/L is a 1-piece heparin-coated titanium (Ti6Al4V ELI) L-shaped implant. The device is 1mm in length, 0.33mm in height (with a 0.25mm high snorkel). The nominal snorkel bore diameter is 120µm and the outer diameter of the snorkel is 0.18mm (the lumen diameter is 0.12mm). The foot is placed within Schlemm's Canal and the snorkel extends through the trabecular meshwork into the anterior chamber, providing an exit route. The device is Heparin-coated for purposes of lubrication for self-priming to establish initial flow. There stents are directional (i.e., there is a left-flow and right-flow model; they are identical, but the foot faces opposite directions on each model) to shunt fluid toward largest concentration of collector channels of each eye.

The device is supplied pre-loaded on a disposable single-use applicator (see Figure 2) in a sealable/sterilizable tray. The portion that contacts the eye is stainless steel. The devices are sterilized by gamma irradiation and have a shelf life of three years.

The stent is designed for ab-interno implantation for insertion into the nasal trabecular meshwork to allow fluid to flow into Schlemm's Canal and into the normal physiologic outflow pathways (i.e., collector channels and episcleral veins).

3 Proposed Indications for Use

The applicant proposed the following indication:

The iStent® Trabecular Micro-Bypass Stent Model GTS100R/L is indicated for use in conjunction with cataract surgery for the reduction of IOP in subjects with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

Panel members will be asked if the data presented in this PMA support this indication.

4 Regulatory History

The original stent design was studied under: protocols GC-001B, GC-001A, GC-002, and GC-004 and US IDE #----------(protocol GC-001B). The previous version of the stent had a different tip design than that used in the PMA study. According to the applicant, the older tip was not as sharp and resulted in more difficulty penetrating through the meshwork to reach Schlemm's canal, resulting in a higher rate of malpositioned stents. Both the stent and the inserter were modified prior to initiation of the PMA clinical trial; the stent tip was redesigned to improve insertion and the internal components of the inserter were re-designed in an effort to reduce sticking of the inserter trigger.

The PMA cohort clinical study of the iStent GTS 100R/L was conducted under IDE # ---------- originally submitted in July, 2004. This study was a randomized, concurrently controlled pivotal clinical trial that also had a third non-randomized arm. As of the writing of this Summary the IDE remains open, but enrollment has been closed. All active subjects continue to be followed. Following submission of this PMA by the applicant, FDA issued a major deficiency letter indicating that the PMA lacked the information needed to complete the review. The applicant responded to our letter and further interactions between FDA and the applicant since that time led to additional data analyses presented in this PMA executive summary.

5 Pre-clinical Studies

5.1 Biocompatibility

Testing was performed on the stent (or representative samples of the finished device), and included cytotoxicity testing, acute systemic toxicity testing, irritation/sensitization testing, muscle implant studies, genotoxicity testing and material-mediated pyrogen testing. In addition, biocompatibility testing was also performed on the patient-contacting portion of the inserter.

Physico-chemical tests, such as tests for extraction in aqueous and in organic solvents, and hydrolytic stability were not performed. The applicant states that there is an "extensive history of titanium use in medical device, the titanium material contains no monomers, and titanium is not subject to hydrolytic degradation."

Lastly, Fourier Transfer Infrared spectroscopy was performed to evaluate the heparin coating. In addition, analysis of the heparin coating content and contact angle was performed.

Biocompatibility testing is summarized in Table 1.

5.2 Sterilization, Packaging and Shelf Life

The iStent is sterilized by gamma radiation. The device is packaged for sterilization and placed into a cardboard shipping box and transported to a contract sterilization facility. Each box is exposed to 25 – 40 kGy of gamma radiation. Sterilization validation was performed to validate the irradiation dose and to confirm that a sterility assurance level (SAL) of 10-6 is achieved.

In addition to the SAL validation, Glaukos conducted a bioburden validation and irradiation dose audit. Other tests include bacteriostasis/Fungistasis testing, limulus amoebocyte lysate (LAL) testing, bacterial endotoxin testing and inhibition/enhancement testing.

Regarding the final packaging, Glaukos conducted accelerated shelf-life studies to qualify a 3-year shelf-life (real-time aging should be completed). Additional package integrity testing was done to verify adequate microbial barrier (seal strength and dye penetration or bubble leak test) and qualification during shipping (transportation studies/simulation).

5.3 Engineering Bench Testing

Glaukos evaluated the stent with respect to physical and mechanical requirements as outlined in ANSI Z80.27-2001. Tests for surface quality, dimensions, physical stability, pressure/flow characteristics and structural integrity were performed.

Specifically, in-vivo physical stability testing was completed to evaluate the functional and dimensional stability of the iStent. The structural integrity of the device was studied to evaluate the stress levels during the highest anticipated load conditions for the stent.

Pressure and flow characteristics were evaluated to determine theoretical resistance and to characterize the capability of the device to function under decreasing pressure gradients as well as under conditions of negligible pressure difference.

Lastly, insertion testing was completed to evaluate the device and insertion ability. Additional testing was also performed to demonstrate whether the inserter could reacquire the stent after implantation. The insertion tool, itself, was tested to evaluate trigger actuation forces and trigger sticking.

5.4 Manufacturing (M070012, Module 3)

The Glaukos iStent is manufactured from titanium. The manufacturer performs the micro-machining process to make the implants in accordance with Glaukos specifications as a single-piece device. After cleaning, a sample undergoes visual inspection for the presence of burrs. The device is then coated with porcine-derived heparin. After the stents are covered with heparin, all stents are inspected and then stored in a desiccant chamber.

The inserter is assembled and after attachment of the stent, is placed into a packaging tray, which is placed into an outer blister tray and sealed with a Tyvek lid. The devices are then packaged for sterilization using a shipping box carton. The devices are gamma sterilized.

Prior to release, the device history records (DHR) are inspected to ensure they are complete and accurate. The final release criterion requires the results from the Limulus Amoebocyte Lysate (LAL) testing, package peel strength testing and sterilization records be reviewed prior to release of product. Retention samples are removed from each lot, labeled as such and moved to a designated area.

6 Clinical Studies

6.1 Outside of United States (OUS) Clinical Studies

6.1.1 OUS Studies Done with Prior Models

Clinical studies with the original design of the device iStent GTS 100R/L were performed under protocols GC-001B, GC-001A, GC-002, and GC-004 and US IDE #----------(protocol GC-001B). Please see Appendix 2 for the summary.

Due to differences in device design and study populations, FDA does not consider these studies in the evaluation of key safety and effectiveness outcomes for the subject device of this PMA.

6.1.2 OUS Studies Involving the Current Stent and Inserter Design

OUS studies of the current model of the device were conducted under the following protocols:

- GCF-005: conducted in the EU and Turkey, studying subjects with open angle glaucoma randomized to receive either 1 or two stents
- GCF-006: conducted in Turkey, studying subjects randomized to receive either the device (2 stents) or glaucoma medications
- GCF-007: conducted in the EU and Turkey, studying subjects with newly diagnosed open-angle glaucoma, ocular hypertension, or mild glaucoma randomized to cataract surgery + implantation with 2 stents or cataract surgery + medications.

A summary of these studies and additional information regarding OUS implantation of the device can be found in Appendix 3.

Due to differences in the study populations and the use of the device (e.g., multiple stent insertions) in the OUS studies, FDA is considering the IDE study as the primary basis for the evaluation of safety and effectiveness. However, FDA considers the OUS studies as additional supportive evidence.

6.2 PMA Cohort Clinical Study

This PMA contains data from three arms examined under IDE ----------

- The first two arms comprise a prospective, randomized, open-label, multi-center, controlled clinical trial conducted at 27 U.S. investigational sites. Randomized population consisted of 240 eyes of 239 subjects (117 treatment eyes of 116 subjects and 123 control eyes of 123 subjects).

- The third arm is a non-randomized cohort of an additional 50 subjects at 10 sites included for safety evaluation.

The main effectiveness evaluations were performed on the randomized arms. Safety was evaluated using all subjects. The enrollment criteria and methods used in all three arms of the study were the same. Study duration was two years, with primary effectiveness endpoints evaluated at 12 months postoperatively.

6.2.1 Brief Overview of the IDE Clinical Study

6.2.1.1 Effectiveness -- Randomized Clinical Trial

The trial was a prospective, randomized, open-label, multi-center, controlled clinical trial conducted at 27 U.S. investigational sites. Study duration was two years, with primary effectiveness endpoints evaluated at 12 months postoperatively. Subjects were diagnosed in the study eye with mild to moderate open-angle glaucoma (OAG), or pseudoexfoliative and pigmentary glaucoma.

Main Effectiveness Endpoints:

- Primary: the proportion of subjects with IOP ≤ 21 mmHg without use of antiglaucoma medication at 12 months.
- Secondary: the proportion of subjects with an IOP reduction from baseline of ≥ 20% without use of anti-glaucoma medication at 12 months.

The results for both of these efficacy outcomes were compared between the two study groups, based upon an Intent-to-Treat (ITT) analysis.

The study eye was required to have:

- Medicated IOP of ≤24 mmHg at screening evaluation
- Unmedicated IOP ≥ 22 mmHg and≤36 mmHg at baseline visit, after washout.
- Clinically significant cataract.

If meeting all inclusion/exclusion criteria, subjects were randomized. Subjects were randomized 1:1 into either the treatment group (implantation of the iStent into the nasal trabecular meshwork in conjunction with cataract surgery) or the control group (cataract surgery only). Following surgery, patients were examined at 3-7 hours, 1 days, 1-2 weeks, and 3, 6, 12, 18 and 24 months following post-op.

All IOP measurements at follow-up visits were to be taken at approximately the same time of day (± 2 hours). In order to prevent bias in the measurements, IOP measurement was carried out in a blinded fashion. The protocol instructed investigators that anti-glaucoma medications should

be added in a consistent manner in both the treatment and control groups based on IOP, optic nerve and visual field status, and only when necessary to control IOP. After the baseline evaluation, there was no washout of medications for tonometry. (I.e., after anti-glaucoma medication was re-introduced, non-medicated IOPs were never assessed.)

Results:
The two arms comprised a population of 240 eyes of 239 subjects (117 treatment eyes of 116 subjects and 123 control eyes of 123 subjects). At baseline, mean non-medicated IOP was 25.2 mmHg, and 25.5 mmHg in the Control. In the Treatment arm, 111 subjects were implanted with an iStent, 106 completed the 12 month postoperative visit and 104 completed the 24 month visit. In the Control arm, 117 had cataract surgery, 112 were seen at 12 months postop, and 107 at 24 months.

Primary Endpoint: At the 12 month postoperative visit, the numbers of eyes with IOP ≤ 21 mmHg without medication were:
- Treatment Group (iStent): 79 (of 116 enrolled) – 68.1%,
- Control Group: 61 (of 123 enrolled) – 49.6%.

In a 1-sided z-test of the difference in proportions, the p-value was 0.003

Secondary Endpoint: At 12 months, the numbers of eyes with IOP reduction from baseline ≥ 20% without medication were:
- Treatment Group: 74 eyes (of 116 enrolled) – 63.8%,
- Control Group: 58 eyes (of 123 enrolled) – 47.2%.

In a 1-sided z-test of the difference in proportions, the p-value was 0.007

There was no statistically significant difference between groups at the 24 month postoperative time point for either the primary or secondary effectiveness endpoints when missing data were handled by methods other than last-observation-carried forward.

Note: FDA evaluated whether the manner in which anti-glaucoma medications were re-introduced may have affected the primary effectiveness outcomes. Looking at the last available non-medicated IOPs in subjects who were "rescued" with anti-hypertensive medication:
- For the Treatment Group: 2 of 18 rescued subjects had medication re-introduced with unmedicated IOP ≤ 21, and
- For the Control Group: 11 of 41 rescued subjects had medication re-introduced with unmedicated IOPs ≤ 21.

For the subjects available at 12 months postoperatively, the last available non-medicated IOPs are summarized as follows:
- Treatment Group: Mean = 19.2 mmHg; Median = 17.5 mmHg;
- Control Group: Mean = 21.1 mmHg; Median = 18 mmHg.

6.2.1.2 Safety

In addition to the randomized study arms described above, the applicant added to the study a non-randomized cohort of an additional 50 subjects, included for additional safety data. (10 sites, 1 of which was not in the randomized study.) Forty-six (46) subjects were successfully implanted with the iStent. The enrollment criteria and methods used in this arm of the study were the same as those used in the randomized study. Forty-four (44) were seen at the 12-month visit, and 44 at the 24-month visit.

In both randomized arms and in the non-randomized arm, there were the types of adverse events commonly seen in all studies involving cataract surgery. While it is difficult to definitively attribute some events directly to the stent (for example, uveitis), the following adverse events are clearly stent related:

- Stent obstruction by iris, vitreous, fibrous overgrowth, fibrin, blood, etc.: 5 randomized treated subjects (4%) and 2 non-randomized treated subjects (4%)
- Stent malposition: 3 randomized treated subjects (3%) and 2 non-randomized treated subjects (4%)

There were a number of secondary surgical interventions related to iStent placement in the randomized and non-randomized treatment subjects. In the randomized arms, Stent-related secondary surgical interventions were reported in 5 subjects (3 with stent repositioning, 1 with stent removal and replacement, 1 with laser iridoplasty) to resolve stent obstruction or malposition observed by investigators in the early postoperative period. There was 1 such event in the non-randomized arm (Nd:YAG for stent obstruction). Thus, the rate of secondary surgical interventions that were clearly device-related, in the combined iStent arms was 6/162 (3.7%). If the laser interventions are eliminated, the rate was 4/162 (2.5%). [For a benchmark, the ISO IOL "grid" indicates an historical rate for all secondary surgical interventions (excluding posterior capsulotomies) of 0.8%. This historical rate is for cataract surgery alone.]

6.2.2 Study Objectives

The study objective was to assess efficacy and safety of the iStent Trabecular Bypass Microstent when used in conjunction with cataract surgery in subjects with mild to moderate open angle glaucoma.

6.2.3 Study Endpoints

6.2.3.1 Effectiveness Endpoints:

- Primary: the proportion of subjects with IOP ≤ 21 mmHg without use of antiglaucoma medication at 12 months.
- Secondary: the proportion of subjects with an IOP reduction from baseline of ≥ 20% without use of anti-glaucoma medication at 12 months.

The results for both of these efficacy outcomes were compared between the two study groups, based upon an ITT analysis.

6.2.3.2 Safety Endpoints

Anticipated and unanticipated adverse events were to be collected and recorded.

6.2.4 Eligibility Criteria

6.2.4.1 Inclusion Criteria

All Inclusion Criteria applied to the study eye only except where indicated.

- Subjects were to have been diagnosed with mild to moderate open angle glaucoma (OAG). This included Primary Open Angle Glaucoma (POAG), and the secondary open angle glaucomas Pseudoexfoliative Glaucoma (PXG) and Pigmentary Glaucoma (PG).

Diagnosis was based on the following functional and structural parameters:

- Mild to moderate OAG diagnosis based on the following:

A. C:D Ratio: Given the requirement for early stage glaucomatous disease, the subject's cup-disc ratio (C:D) must have been ≤ 0.8. Additionally, the subject had to qualify by having visual field defect as described in "B" OR characteristic nerve anomaly as described in "C" (below).
B. Visual Field criteria (VF): In case of visual field defect, the following criteria must have been met:
   - No severe nasal steps worse than 4 continuous clustered points
   - No more than 3 clustered points with sensitivity less than 15dB within 15 degrees from the fixation point
   - No other evidence at clinical examination of moderate to advanced nerve fiber bundle defects (i.e. Bjerrum scotoma)
C. Characteristic nerve abnormalities consistent with glaucoma: One or more of the following was acceptable for diagnosis:
   - Segmental loss of neuroretinal rim (notching)
   - Drance disc hemorrhage (splinter hemorrhage)
   - Nerve fiber layer loss (as observed with an ophthalmoscope)
   - Pseudo pit of the disc
   - Visible laminar dots
   - Optic nerve abnormalities determined by confocal scanning imaging (HRT)
   - Findings on polarimetry consistent with early glaucoma such as a wedge shaped-defect connecting to the optic nerve head with values at or below the 5th percentile as evidenced on the deviation map, any parameter below the 5th percentile, or the NFl >35 (GDx).
   - Findings on OCT of RNFL (Retinal Nerve Fiber Layer) thickness outside of the normal range consistent with clinical evaluation of the optic nerve and RNFL.

- BCVA 20/40 or worse with medium BAT and clinically significant cataract eligible for phacoemulsification
- Subject taking at least one ocular hypotensive medication, but not more than three medications, with a stable prescription for at least 2 months and able to undergo a washout (study eye only).
- Medicated IOP of ≤24 mmHg at screening evaluation
- Unmedicated IOP ≥ 22 mmHg and≤36 mmHg at baseline visit, after washout

- Gonioscopy confirming normal anatomy for cataract eyes (excluding peripheral anterior synechia (PAS), rubeosis or other angle abnormalities that can lead to improper placement of the stent)
- Able and willing to attend follow-up visits for two years postoperative
- Able and willing to sign informed consent

6.2.4.2 Exclusion Criteria

Subjects were excluded from the study for the following reasons:

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

According to a flowchart provided in the protocol, if the subject experienced “Cataract Surgery Complications,” during the operative procedure, he would be exited from the study and a Study Summary Form would be completed. If no complications occurred, the subject would continue with regularly scheduled study follow up.

6.2.5 Sample Size Determination

For Effectiveness: The applicant calculated the sample size necessary to show a significant difference between test and control groups for the primary effectiveness endpoint of the proportion of subjects with 12 month IOP ≤ 21 mmHg without medication. Assuming a responder rate of 55% for the Treatment Group and 35.5% for the Control Group, the applicant determined that a sample size of 90 for each group would provide 80% power to detect this difference in rates. They chose to enroll approximately 110 per arm of the randomized study, in order to account for possible subject drop-out.

For Safety: The applicant did not power the IDE study to evaluate any specific level of risk.

In order to provide a benchmark, we provide the following information:

> In PMA studies for new intraocular lenses, applicants provide data from 300 subjects available through 1 year postoperatively. The rationale for 300 subjects is to provide a sufficient sample size so that the study is likely to reveal the presence of any type of adverse event – even of those types that are completely unexpected – that would be present in the implanted population at a rate of 1% or greater, This sample size is based upon the statistical "Rule of Threes," which states that if no events are observed in n subjects, a 95% confidence upper limit on the rate of occurrence is 3/n. Thus, if no adverse events are seen in a sample size of 300, there is 95% confidence that the rate of occurrence is <1%.

As mentioned above, after the randomized portion of the study was in progress, the applicant decided to enroll an additional 50 non-randomized subjects for implantation with the iStent, in order to collect additional safety data.

Thus, using the "Rule of Threes" for the IDE study, if no events of a particular type are seen in a sample size of 150, a 95% confidence upper limit on the rate of occurrence in the population is 2%. For example, if no cases of endophthalmitis were to be seen in a sample of 150, the true rate could reasonably be expected to be as high as 2%.

6.2.6 Subject Entry, Examination Schedule, and Procedures

The plan for subject flow through the study from screening through exit is depicted in Figure 4 and further described in the text in this section.

6.2.6.1 Screening

Subjects signed an Informed Consent Document (ICD) and underwent an initial screening examination to determine their study eligibility at this visit. The subject was then allowed to enter the washout period. If deemed ineligible, the subject was exited from the study.

6.2.6.2 Washout

Subjects qualifying for washout ceased use of all topical IOP lowering medications in the study eye. The washout period varied according to the particular medications the subject was using.

The minimum washout period required for each medication was provided to investigators by the applicant.

6.2.6.3 Baseline

Following washout, the subject underwent a baseline visit during which additional testing was performed and it was confirmed that the unmedicated IOP was within the required range of ≥ 22 mmHg and ≤ 36 mmHg. If criteria were not met, the subject was exited from the study. If the subject met the requirements, he was scheduled for surgery. Subjects were randomized at this visit to Group 1 (treatment group, cataract surgery + iStent implantation) or Group 2 (control group, cataract surgery alone).

6.2.6.4 Operative Procedure

A specific preoperative antibiotic regimen was required. Clear corneal incision with standard phacoemulsification techniques was the recommended procedure for cataract removal. Use of a capsular tension ring to provide capsular stability was allowed in PXG subjects. Use of limbal relaxing incisions for correction of astigmatism was also allowed. Neither was considered likely to impact IOP measurements.

Successful, uncomplicated cataract surgery was required for each subject in the study, regardless of study group. If there were complications during the cataract surgical procedure that would be significant enough to impact the study results (for example vitreous removal/vitrectomy, severe corneal injuries, or other complications), the subject was to be exited from the study.

Insertion of the iStent was performed from the temporal side of the head and the stent was inserted into the nasal trabecular meshwork under gonioscopic guidance. A right- or left-flow stent was used in the respective eye. The surgeon was instructed in how to locate an area in the nasal meshwork that could represent an area of collector channels; slide the leading edge of the device through the meshwork and into Schlemm's canal; and release the device from the inserter. If difficulty was encountered, the surgeon was instructed to move inferiorly for each subsequent attempt. Proper placement was confirmed by gonioscopic examination at high magnification.

Post-operative Management

All subjects underwent IOP measurement 3-7 hours after surgery. IOP lowering medication was allowed at this time if the observed IOP at this time was ≥ 10 mmHg above the baseline IOP value. The protocol provided the general guidance that medications should be considered when unmedicated IOP reached >21 mmHg. However, it should be noted that if there were elevated IOP requiring medication after surgery, medication could be added at the investigator's discretion. Types of medication and criteria for adding them were not specified in the protocol. A pressure spike could be treated with wound "burping" as needed.

Specific instructions regarding medication use and eye shielding in the immediate post-operative period were provided. A tapering dose of topical fluoroquinolone antibiotic and prednisolone acetate 1% was to be used following a set schedule. However, at one month postoperative, investigators could decide to discontinue the medication taper at their discretion.

6.2.6.5 Subject Follow-up

All subjects were to participate in scheduled follow up visits through two years of follow up. Subjects were reexamined at Postoperative day 1, 1-2 weeks, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months according to a specified schedule of visit windows. Evaluations occurring outside the specific visit window period would be considered protocol deviations. Table 2 and Table 3 summarize the evaluations performed at each study visit and the visit window for each study visit.

6.2.6.6 Special Measurement Methodologies

IOP Measurements

All IOP measurements at follow-up visits were to be taken at approximately the same time of day (± 2 hours). In order to prevent bias in the measurements, IOP measurement was to be carried out in a blinded fashion. The reader would use a Goldmann applanation tonometer to measure the IOP, while a second observer would record the measurements. Each time IOP was measured, two measurements would be taken and the mean recorded on the case report form, unless they differed by more than 2 mmHg in which case a third measurement would be taken and the median value would be recorded.

Distance Visual Acuity

At the screening visit, the Snellen BCVA would be measured, and BCVA was required to be 20/40 or worse with medium BAT in the study eye. Vision in the fellow eye was not to be worse than 20/200. At the baseline visit and all subsequent visits, visual acuity was to be measured in LogMAR units using the ETDRS chart. Instructions for performing ETDRS acuity testing were provided in the protocol and a LogMAR conversion table was included. A loss of 5 letters was considered loss of one line of vision.

Visual Fields

Visual fields were to be measured using automated threshold visual field testing with the SITA-Standard algorithm. However, if a visual field performed within 6 months prior to screening evaluation was used as the initial field, then the test used would be indicated on the screening form and SITA –Standard would be the testing algorithm used at the baseline evaluation and for each test after that. The protocol required that the same testing program be used for that subject for each test taken in the study. Visual fields were required to have less than 33% false errors and fixation losses. If pupil dilation was required for baseline visual field testing because the pupil was < 3mm in diameter, then it was to have been used at all subsequent visual field tests.

Pachymetry

Pachymetry was to be performed three times at the baseline exam with an electronic pachymeter and the 3 measurements averaged. The mean baseline value was to be recorded. Follow-up pachymetry would be performed at the 12 and 24 month visits following the same procedure as at the baseline visit.

6.2.7 IDE Study Population Description and Accountability

The IDE study population is comprised of three arms: a randomized control group receiving cataract surgery alone; a randomized treatment group receiving cataract surgery with iStent implantation; and a non-randomized group receiving cataract surgery with iStent implantation.

Two-hundred and forty (240) eyes of 239 subjects were randomized to undergo either the iStent procedure in conjunction with cataract surgery (randomized treatment group = 117 eyes of 116 subjects) or cataract surgery without the iStent procedure (randomized control group = 123 eyes of 123 subjects). The randomized subjects comprise the effectiveness population of this study. An additional 50 non-randomized subjects were enrolled to undergo the iStent procedure in conjunction with cataract surgery for further evaluation of safety. FDA further combined the non-randomized treatment subjects with the randomized treatment group for safety evaluation.

The randomized phase of the IDE study has been completed with 24-month follow-up of all subjects.

At the time of this writing all subjects in the non-randomized phase of the IDE study have been followed through the 24-month visit, but at the time of PMA submission, subjects were still active (6 subjects had been seen at the 24-month visit and 39 were still active). The applicant provided an update of the adverse events that had occurred up to the time of the writing of this Executive Summary.

As stated in the sample size section, with 150 iStent subjects in the IDE study, if no occurrences of any particular type of adverse event are seen in the study, the true rate could reasonably be expected (with 95% confidence) to be as high as 2%. Given this statistical fact, the panel will be asked whether they believe the sample size of the IDE study (along with any supportive data from the OUS studies) is sufficient to provide a reasonable assurance of the safety of this implantable device.

6.2.7.1 Accountability

6.2.7.1.1 Accountability of Randomized Subjects

Figure 5 and subsequent text describes the disposition of the eyes (not subjects as indicated in the table provided by the applicant) in the randomized population.

Treatment (iStent) Group

One hundred and seventeen (117) eyes of 116 subjects were randomized to the treatment group. One-hundred and eleven (111) of these eyes underwent cataract surgery with iStent implantation; a stent was not implanted in 4 eyes due to cataract surgery complications (one of which was the first eye of the subject for whom both eyes were enrolled) and was not implanted in 1 due to inability to implant the stent; one subject was terminated from the study prior to undergoing treatment.

Of the 111 subjects implanted with the iStent, 106 completed the 12-month postoperative visit; 1 subject missed the visit, 2 died, and 2 withdrew due to poor health (one by the subject and one by the investigator). One hundred and four (104) completed the 24-month visit; 2 more subjects died, and one subject was lost to follow-up.

Control Group

One hundred and twenty-three (123) subjects were randomized to the control group. One hundred and seventeen (117) of these underwent cataract surgery; 4 withdrew consent prior to surgery; one failed the baseline exam; one terminated the study prior to treatment. One hundred

and twelve (112) subjects were evaluated at the 12-month visit. Three subjects exited the study after cataract surgery due to complications of the surgery, one subject died, and one subject withdrew from the study. One hundred and seven (107) were seen at the 24-month visit. One subject was lost to follow-up, 3 subjects discontinued the study on their own accord (2 due to poor health and 1 moved away), and 3 subjects total died during the course of the study.

6.2.7.1.2 Accountability of Non-randomized Subjects

Fifty (50) subjects were enrolled. Forty-eight (48) subjects underwent cataract surgery with iStent implantation; 2 subjects withdrew consent prior to surgery. Forty-six (46) subjects were successfully implanted with the iStent, and the stent could not be implanted in 2 subjects. Forty-four (44) subjects were seen at the 12-month visit; one subject died, and one subject missed the visit. Forty-four (44) subjects were seen at the 18-month visit, and 44 were seen at the 24-month visit. A total of 2 subjects were discontinued by the 24-month visit.

6.2.7.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics of the subjects are summarized in Table 4 - Table 6. For the randomized arms, the mean unmedicated IOPs were 25.2 mmHg (Treatment Group) and 25.5 mmHg (Control Group).

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

Table 4 accounts for 116 eyes of 116 subjects (for medicated and unmedicated IOP at baseline). One eye (----------) was excluded from this table, since that eye was one of 2 eyes of the same subject that was excluded from the effectiveness analyses discussed below for reasons of correlation between the two eyes of the same subject. This table also includes all 50 eyes of 50 subjects enrolled into the non-randomized treatment group.

Please note that in Table 5, for the randomized population the descriptive statistics are based on all eyes (not excluding ----------), and that Table 6 for the non-randomized population excludes 2 subjects who withdrew consent prior to surgery and 2 subjects in whom the stent could not be implanted.

6.2.7.2.1 Characteristics of Randomized Treatment (iStent) Group

As outlined in Table 4, of the 116 subjects in the randomized treatment group, 68% were 70 years of age or older. The age of the randomized treatment group ranged from 53 to 88 years old, with a mean age of 74 years. There were more female than male subjects, i.e., 60% percent of subjects were female. The majority of subjects (71 %) were White, with the remainder of the population comprising Hispanic or Latino (14%), Black or African American (13%), American Indian or Alaska Native (1 %), Asian (1 %) and Native Hawaiian or Pacific Islander (1 %) subjects. There were 59 right eyes and 58 left eyes.

6.2.7.2.2 Characteristics of Randomized Control Group

Similar demographic characteristics were seen in the 123 randomized control subjects. Sixty-five percent were 70 years of age or older. The age of the control group ranged from 48 to 88 years

old, with a mean age of 73 years. Fifty-eight percent were female. The majority of subjects (72%) were White, with the remainder of the population comprised of Black or African American (15%), Hispanic or Latino (12%) and American Indian or Alaska Native (1%) subjects. There were 61 right eyes and 62 left eyes.

6.2.7.2.3 Characteristics of Non-randomized Treatment (iStent) Group

Similar to the randomized subjects, 74% of the non-randomized subjects were 70 years of age or older, with a mean age of 73 years. Sixty-two percent of subjects were female. The majority of subjects (60%) were White, with the remainder of the population comprising Hispanic or Latino (32%), Black or African American (6%) and Asian (2%). Slightly over half (54%) of the 46 eyes that underwent cataract surgery with iStent implantation were right eyes.

The panel members will be asked whether they believe that the safety and effectiveness outcomes are expected to reasonably represent those that are anticipated once the device is marketed in the U.S. (when used according to the proposed indication for use) given the distribution of the demographic and baseline characteristics of the study subjects, particularly race.

6.2.8 Operative Procedure

The cataract operative procedures were similar for the 2 randomized groups (e.g., clear corneal incisions were used in 94% of treatment and 93% of control eyes), except that intracameral miotics were used more often in the treatment group (64% vs. 24% in the control group), and topical anesthesia was used more often in the control group (61% vs. 38% in the treatment group) rather than peribulbar or retrobulbar blocks.

Stent implantation was attempted in 112 subjects randomized to the treatment group, and was unsuccessful in 1 subject after 2 attempts due to "poor visualization and shallow angle secondary to moderate arcus." Of those subjects that had successful implantation, 62% were successful on the first attempt and 28% were successful on the second attempt. Eight of 111 subjects had successful implantation of the stent on the third attempt, and 3 required 4 or more attempts in order to successfully implant the device.

Difficulty implanting the stent was rated on a scale of 1-5 with one being the least difficult. It is interesting to note that in the case where the stent was not successfully implanted the difficulty was rated as 4 rather than 5. About 1/3rd of cases (35/111) were rated with a difficulty of 3 or higher.

Non-randomized Population:

Of the 46 subjects in the non-randomized population implanted with the iStent, clear corneal incisions were used in 96% of cases, intracameral miotics were used in 76% of cases, and topical anesthesia was used in 41% of cases. Of the 46 subjects that had successful implantation, 57% were successful on the first attempt and 30% were successful on the second attempt. Three subjects had successful implantation after 3 attempts, and 3 required 4 or more attempts in order to successfully implant the device. Eight of the 46 cases were rated with a difficulty of 3 or higher.

6.2.9 Protocol Deviations

Protocol deviations were described for both the randomized and non-randomized cohorts of the study.

6.2.9.1 Randomized population

There were

- 22 enrollment deviations
- 16 deviations related to informed consent
- 29 deviations related to the intraoperative procedure
- 154 instances of clinical assessments not being performed at the scheduled visit
- 47 instances of follow-up visits being performed outside the visit window. None of these "out of window" visits occurred at the 12 month exam.

The protocol deviations for the randomized population are summarized in Table 7. Additional details about certain deviations are provided in the text.

There was one subject in the randomized treatment group in whom two stents were implanted. The first stent was placed in the scleral spur inadvertently, so a second stent was placed in Schlemm's canal at the time of the initial surgery.

Additional Information Regarding Selected Deviations Related to Enrollment

Of the 22 protocol deviations that occurred in 22 subjects (14 treatment and 8 control), 6 subjects (3 treatment and 3 control) had the randomization envelope opened out of sequence. All of these subjects underwent the treatment specified in the envelope opened. Of the 4 subjects that had enrollment deviations related to the fellow eye, one subject's fellow eye had already been enrolled into the study (that eye was later exited after cataract surgery complications, prior to stent implantation).

6.2.9.2 Non-randomized population

Protocol deviations for the non-randomized population are summarized in Table 8 and Table 9. There were no deviations related to eligibility in the non-randomized group.

There was only one visit outside visit window for the 12-month visit, and seven other visits outside visit windows. Of these seven additional visits outside of the window period, the greatest deviations were 23 days outside of the 3 month visit window and 45 days outside of the 6 month visit window.

6.2.10 IDE Clinical Study Outcomes and Analyses

6.2.10.1 Safety Results and Analyses

The protocol defined the safety population as all subjects who underwent cataract surgery, with or without iStent® implantation, with the data analyzed according to the actual treatment each subject received. Because this definition does not allow for comparisons of intraoperative complications among treatment groups, since subjects who had significant intraoperative cataract surgery complications were not to receive the iStent, FDA asked the applicant to provide safety analyses for all eyes in which surgery was attempted according to the treatment group to which the eye was assigned. This modified definition does not change the postoperative safety

population, since postoperative safety data is missing for eyes randomized to iStent implantation that were discontinued from the study without receiving the iStent due to cataract-surgery-related intraoperative complications and/or inability to implant the stent.

6.2.10.1.1 Adverse Events
6.2.10.1.1.1 Intra-operative Adverse Events
6.2.10.1.1.1.1 Randomized Population:
Complications related to cataract extraction and IOL implantation were reported in 9 eyes (5 treatment and 4 control):

- inadvertant loss of vitreous or vitrectomy: 5 treatment eyes:
  - four were exited from the study
  - one was implanted with the stent (considered a protocol violation)
- inadvertant loss of vitreous or vitrectomy : 3 control eyes
  - all three were exited following the surgery.
- torn IOL haptic and IOL exchange at the time of surgery: 1 control eye.
  - this one eye was not exited and was counted as a protocol violation.

There were 12 reports of intra-operative complications related to implantation of the iStent:

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

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

6 subjects in the non-randomized population reported intra-operative complications related to iStent implantation.

- In two cases, stent implantation was unsuccessful after several attempts due to "poor visibility" (#-------- and --------). These subjects were exited from the study after surgery.
- Four additional subjects experienced intraoperative complications:
  - One required 4 attempts to insert the device and experienced anterior chamber collapse, iris touch by the device, and pain during insertion.
  - In one subject, the stent was implanted in the incorrect location (behind the iris insertion between the ciliary body and the sclera) and iris touch and damage were reported due to the stent being inadvertently inserted through a small iridodialysis. This subject complained of early postoperative pain that resolved.
  - One subject was reported to have had the corneal endothelium touched by the device,
  - One subject was reported to have had the iris touched by the device.

All 4 of these additional intraoperative complications had resolved with BCVA of 20/40 or better at the last study visit.

6.2.10.1.1.2 Postoperative Ocular Adverse Events

6.2.10.1.1.2.1 Secondary Surgical Procedures

Table 11 outlines the secondary surgical procedures that were performed in the randomized and non-randomized populations. Information regarding selected procedures is provided in the text.

Additional explanation of selected secondary procedures in the Randomized Population:
Treatment group:

- Laser iridoplasty in one case for iris obstruction of the stent at 1 day postoperative.
- 3 reports of stent repositioning
  - Two were due to inadequate clearance noted between the stent and the iris postoperatively
  - One was due to the stent not being in Schlemm's canal postoperatively.
- One report of stent removal and replacement, due to the stent not being in Schlemm's canal.
- One underwent argon laser treatment for diabetic macular edema.

Control group:

- One subject in the control group that underwent deep sclerectomy and deep sclerostomy.
- One underwent pupilloplasty to treat symptoms of glare, halos, and decreased vision associated with an enlarged pupil postoperatively. This subject also had repair of a wound leak and IOL removal and replacement after the initial surgery due to complaints of poor near visual acuity. This was the same subject that had a torn haptic intraoperatively requiring removal and replacement of the IOL intraoperatively.
- One underwent LASIK for residual postoperative hyperopia.
- One underwent vitrectomy for management of macular hole with traction.

Additional explanation of selected secondary procedures in the Non-randomized Population:

- One subject underwent Nd:YAG laser to resolve stent obstruction.
- One subject underwent iris repositioning due to iris incarceration into the surgical wound during the procedure.

6.2.10.1.1.2.2 Postoperative Non-Surgical Ocular Adverse Event

Table 12 summarizes the postoperative adverse events that occurred in the randomized population and the non-randomized population. Further explanation regarding selected events is provided in the text.

6.2.10.1.1.2.2.1 Stent Obstruction/Stent Malposition:

- 5 subjects in the randomized treatment group and 2 subjects in the non-randomized treatment group experienced stent obstruction. Of these, two subjects in the randomized treatment group and one in the non-randomized treatment group underwent secondary surgical intervention to relieve the obstruction (also discussed under Secondary Surgical Procedures):
- One randomized treatment subject (--------) had 2 reports of stent obstruction – once due to blood at 1-day postop with resolution 7 days later and another due to rotation of the stent with obstruction by the iris resolved with stent repositioning.

- One randomized treatment subject (---------) underwent laser iridoplasty on postoperative day 1 to pull the iris away from the stent. At the 1-to-2-week visit inadequate clearance between the iris and the stent was noted. This remained at the subject's last visit at 24 months when the IOP was 20 mmHg on one medication. One non-randomized treatment subject (---------) underwent Nd:YAG laser to remove a membrane-like material from the stent ostium.

Of the 4 additional reports of stent obstruction where surgical intervention was not used:
- In one non-randomized subject (---------) blood was noted to be partially obstructing the lumen of the stent on postoperative day 1. This resolved spontaneously within 8 days.
- In one randomized subject (---------), blood was noted to be obstructing the lumen of the stent on postoperative day 1. This resolved spontaneously within 4 days.
- One randomized subject (---------), had blood obstructing the stent at the 1-to-2-week visit, which resolved spontaneously within 2 weeks.
- In one randomized subject (---------), the stent was reported not be in Schlemm's canal at postoperative day 1 and there was inadequate clearance between the stent and the iris with iris occluding the lumen of the stent. At this subject's last visit at 24 months, the obstruction was still unresolved and the IOP was 20 mmHg on one medication.

There were 3 subjects in the randomized treatment group and 2 subjects in the non-randomized treatment group that experienced stent malposition:
- Two randomized subjects (--------- and ---------) underwent stent repositioning
- One randomized subject (---------) underwent stent removal and replacement.
- One non-randomized subject (---------) was noted to have the stent malpositioned intra-operatively. At this subject's last visit at 24 months, there was no change in location of the stent noted on UBM compared to UBM performed at 1 month postoperatively and the IOP was 13 mmHg on 2 medications.
- One non-randomized subject was reported to have malposition of the stent (in the scleral spur) at 1 month. At the subject's last postoperative visit at 24 months the IOP was 16 mmHg on 2 medications.

6.2.10.1.1.2.2.2 Corneal Edema:

Randomized Population:

Corneal edema was a common finding in the immediate postoperative period. Most edema resolved spontaneously by one month postoperatively. One control eye had corneal edema at 226 days postoperatively. This was deemed to be related to postoperative changes from secondary vitrectomy for macular hole repair.

Non-randomized Population:

As with the randomized group, the most prevalent slit-lamp finding postoperatively was corneal edema in the immediate postoperative period, which resolved by one month. One subject was found to have "folds in Descemet's membrane" and another had "striae." Neither was specifically associated with edema. Both resolved by the next exam.

6.2.10.1.1.3 ISO-defined Adverse Events:

Table 13 summarizes some of the adverse events according to categories that have previously been defined for evaluation of new intraocular lenses at 12- and 24-months postoperatively

respectively. It should be noted that the SPE rate ("the Grid") is based on historical data through one year of follow-up, and not two. It should also be noted that for comparison to "the Grid", IOL data is normally obtained on at least 300 subjects with one year of follow-up following cataract extraction and IOL implantation. There were 5 (4.3%) device/procedure- related secondary surgical interventions in the randomized stent arm of this study and 2 (4.3%) in the non-randomized stent arm. These rates significantly exceeded the IOL Grid rate for secondary surgical interventions for cataract surgery alone. (This data is not included in the applicant's table of ISO defined adverse events as the applicant prepared the table focusing solely on events related to cataract surgery and not including secondary events related to the device itself).

6.2.10.1.2 Other Safety Parameters

The information in this section (except for loss of BCVA ≥ 2 lines at last visit from best BCVA and visual field information) for the non-randomized cohort has not been updated since the cohort completed follow-up through 24 months postoperatively. (Subjects with final BCVA was worse than 20/32 and ≥ 2 lines worse than best BCVA are tabulated in Table 43.)

6.2.10.1.2.1 Increase IOP from Baseline

Randomized Population:

- Thirty-four (34) subjects in the treatment group and 38 controls had increased IOP from baseline of ≥ 10 mmHg. The majority of these increases occurred in the immediate postoperative period and was treated with medication, paracentesis, or both according to the protocol.
- One control subject (--------) presenting with elevated IOP throughout the first 2 months was treated with deep sclerectomy and subsequent laser sclerostomy (as indicated under Secondary Surgical Procedures). Eight days later the subject presented with hypotony (IOP=5) and choroidal detachment (resolved spontaneously within a week). Post-sclerostomy the IOP remained within 5-8 mmHg without medication through the 24-month visit.
- Two control subjects were treated with laser trabeculoplasty.
- One control subject was treated with paracentesis at 24 months for elevated IOP following IOL removal and replacement.
- Two treatment subjects with elevated IOP underwent stent repositioning.

Non-randomized Population:

Twelve subjects in this group experienced IOP increase from baseline ≥ 10 mmHg. All instances occurred in the early postoperative period (postoperative day 1 or earlier) and were treated with paracentesis in all cases and medications in 6 subjects.

6.2.10.1.2.2 Visualization of stent postoperatively:

Visualization of Stent Postoperatively

Randomized Population:

Gonioscopic evaluation was performed only in the stent implantation group. The stent was visible in at least 96% of subjects at all study visits. By 24 months, the stent was not visible in three eyes. Per the applicant, IOP was ≤ 21 mmHg in all three eyes, two of which were on one medication.

Non-randomized Population:
The stent was reported to be not visible by gonioscopy in four eyes at 12 months postoperatively. In all cases, BCVA was 20/42 or better, and IOP was ≤ 21 mmHg on no (2 eyes), one (1 eye), or two (1 eye) ocular hypotensive medications.

6.2.10.1.2.3 Pachymetry

In regard to the tables related to pachymetry, the applicant defined the Safety Population as those eyes that were actually implanted with the iStent for the Cataract Surgery with iStent groups, and those eyes that underwent cataract surgery only for the Cataract Surgery Only group (117 eyes that had been randomized to cataract surgery only and actually received the treatment plus 5 eyes that had been randomized to cataract surgery with iStent implantation but only underwent cataract surgery).

Randomized Population:

For the randomized patient population, mean preoperative corneal thickness was 549 microns in both groups. Table 14, Table 15, and Table 16 show that there appears to be a small increase in pachymetry readings postoperatively from baseline for both groups with a greater increase in pachymetry for the treatment group (cataract surgery with iStent). The greater increase in the treatment group is not statistically significant with regard to the mean change from baseline. However, the pivotal study was not powered to detect such a difference.

Non-randomized Population:
Table 17, Table 18, and Table 19 summarize the pachymetry information available for the non-randomized population. This information has not been updated since subjects have completed follow-up through the 24-month visit. Mean preoperative corneal thickness was 547 microns. At 12 months postoperatively, mean corneal thickness was 552 microns. Information about the change in pachymetry was only provided for the 5 subjects that had pachymetry performed at each visit through 24 months.

Given that the study was not powered to detect differences in pachymetry, and that specular microscopy studies were not included, the panel will be asked to determine whether there is sufficient information to provide reasonable assurance that the addition of implantation of iStent to cataract surgery does not increase the risk to corneal endothelial health beyond that already posed by cataract surgery.

6.2.10.1.2.4 Visual Fields

Randomized Population:
Visual field information was presented in tables as Mean Deviation (MD) and Pattern Standard Deviation (PSD). As indicated in Table 20, the mean [± standard deviation (SD)] pre-operative MD was -3.77 ± 3.03 dB for the treatment group (N=114) and -3.94 ± 3.60 dB for the control group (N=115). At 24 months, the mean (± SD) MD was -3.22 ± 3.01 for the treatment group (N=103) and -3.16 ± 3.66 for the control group (N=104).

Table 21 summarizes the analysis of the change in MD from baseline for the randomized population (e.g., postoperative dB – preoperative dB = change), where:

- An increase MD = postop value increased in a mathematically positive direction ("improvement"), e.g., -5dB preop to -2dB postop = -2 minus -5 = +3 = change > 2 = "improvement", and
- A decrease = postop value decreased ("worsening").

The majority of subjects in both groups had no change (defined as less than 2 db of change) in MD over the course of the study (at 6, 12 and 24 months). At each time point, 16-20% of treatment and 11-15% of controls had decreased MD. Another 23-26% of treatment and 28-33% of controls had increases in MD over the same time period.

As shown in Table 22, the mean (± SD) preoperative PSD was 2.89 ± 1.79 dB for the treatment group (N=110) and 2.79 ± 1.90 dB in the control group (N=112). By 24 months, mean (± SD) PSD was 3.39± 2.29 dB for the treatment group (N=103) and 3.17± 2.51 dB for the control group (N=4). Maximum PSD fluctuated between 11.20dB at baseline to a high of 11.65 dB (at 12 months, decreasing to less than the baseline value at 24 months). In the control group, maximum PSD at baseline was 10.38 dB. Maximum PSD remained increased above baseline throughout the study, reaching a maximum of 13.89 at 6 months postoperative (decreasing to 12.18 dB by 24 months).

Table 23 summarizes the analysis of the change in PSD from baseline for the randomized population (e.g., postoperative dB – preoperative dB = change), where:

- an increase in PSD = postop value increased in a mathematically positive direction, e.g., +3dB preop to +6dB postop = +6 minus +3 = +3 = change > 2, and
- A decrease in PSD = postop value decreased in a mathematically positive direction.

The majority of subjects in both groups had no change (defined as less than 2 db of change) in PSD over the course of the study (at 6, 12 and 24 months). At any given time point, 5-8% of treatment and 4-7% of controls had decreased PSD. Another 10-17% of treatment and 8-13% of controls had increases in PSD over the same time period.

Non-randomized Population:

Visual field information was presented in tables as MD and PSD.

Table 25 summarizes the MD information for the non-randomized population. The majority of subjects had no change (defined as less than 2 db of change) in MD over the course of the study. At each time point, 26-32% of subjects had increased MD. Another 5-14% had decreases in MD over the same time period.

Table 26 and Table 27 summarize the PSD information for the non-randomized population. The mean (± SD) preoperative PSD was 2.48 ± 1.61 dB. By 24 months, the mean (± SD) PSD was 2.98 ± 2.05 dB.

6.2.10.2 Effectiveness Outcomes

6.2.10.2.1 Details Regarding Analysis Issues

During the study, several randomized subjects underwent secondary surgical interventions that could potentially affect the IOP. Initially, the applicant's analyses of effectiveness treated observed outcomes after secondary procedures, including stent reposition, stent explantation/replacement, deep sclerectomy, IOL explantation/replacement, trabeculoplasty, vitrectomy, LASIK, and Nd:YAG laser for stent obstruction, as missing. However, FDA did not agree with this approach. We believed that if a secondary procedure was performed to lower IOP or correct a problem related to the device, then that case should be counted as a failure for purposes of the effectiveness analyses. For the analyses below, FDA treated these as failures.

We discuss these cases in Appendix 1. (Note that paracentesis for IOP control postoperatively and Nd:YAG laser for relief of PCO were allowed in the protocol and were not considered secondary procedures for the purposes of the effectiveness analyses).

Effectiveness Analysis Populations

Intent to Treat (ITT) Population

The primary analysis population for device effectiveness was to be an ITT population, consisting of all randomized subjects in the study, regardless of whether they received the randomly assigned study treatment (with or without iStent). Thus, a patient randomized to receive the stent who did not receive it would be analyzed in the stent group. This population consists of 239 subjects enrolled and randomized at the 27 investigational sites: 116 in the Treatment Group and 123 in the Control Group. One patient in the Treatment Group had both eyes (---------- and ----------) enrolled and treated in the study. FDA believes that eyes from the same patient are highly correlated, and, hence, the outcomes would be expected to be highly correlated. Therefore, it is appropriate to include only one eye (----------) of this subject in the effectiveness analyses. Both eyes were included in the safety assessment, since they both received treatment in the study.

As-treated (AT) Population

The effectiveness analyses were to be performed on the As-Treated (AT) population (randomized cohort), i.e., each subject would stay in the group according to the actual treatment he/she received. For the As-Treated population, the applicant excluded those subjects with major protocol deviations (i.e., not meeting critical eligibility criteria) or with study treatment deviations (i.e., did not receive the study treatment as assigned), or lacking IOP or medication measurements at one year. FDA believes that the applicant's definition of As-Treated population is outcome dependent. Therefore, FDA does not agree with the proposed exclusion and believes that the AT should include 111 subjects (eyes) who received the Cataract Surgery + iStent (Treatment group) and 121 subjects who received the cataract surgery only (Control Group) for effectiveness outcomes.

Missing Data

According to the statistical analysis plan (SAP), the primary and secondary effectiveness outcomes would be calculated and analyzed for the Intent-to-treat (ITT) population of the randomized cohort. Because the ITT population requires the inclusion of all randomized subjects, the applicant proposed these following approaches to address the issue of missing data:

- Last Observation Carried Forward (LOCF) analysis
- Best Reasonable Case analysis
- Worst Reasonable Case analysis
- Non-Responder analysis
- Best Case analysis
- Worst Case analysis

When there is missing data, study results are often analyzed in several alternative manners, in order to assess the robustness of the statistical results.

Because glaucoma devices tend to fail over time, FDA had advised the applicant that the approach of LOCF was clinically inappropriate and, therefore, unacceptable.

The applicant provided definitions of the "Best Reasonable Case" and "Worst Reasonable Case" analyses in IDE ----------.

- In the "Wors---------- nalysis, the observed responder rate of the Control Group was used for those with missing outcomes in the Treatment Group and the observed responder rate of the Treatment Group was used for those with missing outcomes in the Control Group.
- In the "Best Reasonable" analysis, the observed responder rate of the Treatment Group was used for those with missing outcomes in the Treatment Group and the observed responder rate of the Control Group was used for those with missing outcomes in the Control Group. The "Best Reasonable" approach actually extends the responder rates of complete-case data to the missing data.

These approaches, "Best Reasonable" and "Worst Reasonable," were inappropriately named because their definitions were based on the assumption that the responder rate of the Treatment Group will be better than that of the Control Group, which is exactly the study objective and might not necessarily be true. For example, the Worst Reasonable approach may not be as conservative as it sounds if the observed response rate of the Control Group is higher than that of the Treatment Group. Therefore, FDA recommended performing the conventional worst-case and best-case analyses.

- The "Worst Case" analysis assumes missing data as failures in the Treatment Group and successes in the Control Group, and
- The "Best Case" analysis assumes missing data as successes in the Treatment Group and failures in the Control Group.
- The "Non-Responder" analysis assumes all missing outcomes to be failures regardless of treatment arm.

Because of the above concerns about LOCF, Worst Reasonable and Best Reasonable analyses, FDA recommended that effectiveness outcomes be analyzed using the Complete Case (ignoring the missing data), Non-Responder and Worst Case analyses.

The applicant conducted these analyses as requested. However, some of the analysis had slightly different number of subjects (Table 14 through Table 27) than that in the FDA's analyses (Table 28 through Table 37). For example, there were 107 subjects in the applicant's Complete-Case analysis (Table 21) for the primary effectiveness endpoint while the FDA's number was 108 (Table 28). It should be pointed out that such discrepancies in subject numbers do not dramatically change the analysis results.

6.2.10.2.2 Primary Effectiveness Outcomes

In the pivotal GC-003 Study, the statistical hypotheses for the primary effectiveness endpoint were:

$$H_0: P_t \leq P_c$$
$$H_A: P_t > P_c$$

where P_t denotes the proportion of subjects in the randomized treatment group who have IOP ≤ 21 mmHg without use of anti-glaucoma medication at 12 months postoperatively, and P_c denotes the proportion of the randomized control group reaching the same endpoint. [Results were to be analyzed using an ITT analysis (based only upon which arm a subject was randomized to – without excluding any subjects). In the IDE, the applicant had proposed using a LOCF methodology, but FDA did not agree to this. FDA believes that stents often lose effectiveness over time, making it problematic to count any "success" prior to 12 months postoperatively.]

Seventy-nine out of 116 subjects (68.10%) in the treatment group met the primary effectiveness endpoint of IOP ≤ 21 mmHg with no IOP-lowering medications at 12 months postoperatively. In comparison, 61 out of 123 subjects (49.59%) in the control group met the primary effectiveness endpoint. This difference of 18.51% produced a p-value of 0.0040 using a 2-sided Fisher's exact test. (Note that this differs somewhat from the applicant's LOCF analysis.)

Effects of Missing Data:
In order to assess whether results were robust with regard to how missing data were viewed, FDA provides Table 28.The Non-Responder analysis assumes that those who were missing at 12 months are all failures, regardless of their assigned study groups. The Complete-Case Analysis includes all subjects with no missing data at 12 months postop. It is found that both Complete-Case (p=0.0050) and Non-Responder (p=0.0040) analyses provided statistically significant p-values while the Worst-Case analysis yielded an insignificant p-value (p=0.1410) using a 2-sided Fisher's exact test.

Because of the difference in p-values among Non-Responder, Complete Case, and Worst Cases analyses, FDA suggested performing a Tipping-Point analysis to study the relationships among these approaches. Basically, a Tipping-point analysis examines every possible combination of success-failure if the missing data were to be observed. As a result of the Tipping- Point analyses, discussed below, FDA statisticians believe that the main hypothesis testing results are robust, in the sense that the missing data were unlikely to substantially affect statistical conclusions.

Table 29 demonstrates the results of the Tipping-Point analysis. Each cell represents a possible failure/success combination for the missing data. The rows represent the number of assumed successes among the 8 missing subjects in the randomized treatment group. The columns represent the number of assumed successes among the 11 missing subjects in the randomized control group. For example, Cell (5, 6) represents the scenario where there were 5 successes in the Treatment Group and 6 successes in the Control Group among all the missing data. For each case, a test of the primary effectiveness endpoint is conducted between the two study groups and a p-value is generated. The grey color indicates a p-value less than 0.05.

The Worst-Case analysis, known as the most conservative approach to deal with the missing data, is located in the upper right corner of the table. By definition, the Non-Responder analysis assumes all missing outcomes as failures and hence is located in the upper left corner of the table. The cell of "Best Reasonable" represents the case where missing data had the same responder rate of the observed data in the same group. The cell of "Worst Reasonable" demonstrates the case where the missing data in the randomized Treatment Group had the same responder rate of the randomized Control Group and the missing data in the randomized Control Group had the same responder rate of the randomized Treatment Group. These two are located in the middle of the table with "Best Reasonable" having more successes than "Worst Reasonable."

Table 29 shows that for all possible failure/success combinations of the missing data, only a few cases would yield statistically insignificant p-values (the worst-case analysis included as the most conservative) indicating the worst-case analysis may be quite conservative for the primary effectiveness data at 12 months. For example, the results would tip from "significant" to "insignificant" if the situation moved from (0, 7) to (0, 8). The tipping-point analysis shows that the Worst Reasonable analysis always falls in the significant area for all effectiveness analyses and may not be as conservative as it was claimed to be.

"As Treated" Analyses:
Table 30 and Table 31 present the results using the As-Treated (AT) population, i.e. the data set includes subjects in the treatment groups that they actually received treatment. In this study, 111 subjects (eyes) received Cataract Surgery + iStent and 121 subjects received cataract surgery only. The results of the As-Treated analyses are similar to those of the ITT population with the significant p-values of 0.0013 for both the Complete-Case and the Non-Responder analyses. It is noticed that the p-value of the Worst-case analysis is also statistically significant (p=0.0101).

Table 31 presents the results of the Tipping-Point analysis. The significant p-value of the Worst case analysis (p=0.0101) means any failure/success combination would result in a statistically significant p-value. This is why there is no tipping point in the table.

The panel will be asked which approach for handling missing data should be relied upon to assess effectiveness, one of the approaches discussed (including Last-Observation-Carried-Forward) or some other approach.

Results at 24 Months Postop:
Table 32 and Table 33 present the results of data at 24 months using the "analyses based upon randomization" and As-Treated analyses, respectively. None of the tests demonstrated statistically significant device effectiveness at 24 months.

6.2.10.2.3 <u>Secondary Effectiveness Outcomes</u>
The statistical hypotheses for the secondary effectiveness endpoint were:

$$H_0: P_t \leq P_c$$
$$H_A: P_t > P_c$$

where P_t denotes the proportion of subjects in the randomized Treatment Group with IOP percentage reduction from baseline ≥ 20% without use of IOP-lowering medication at 12 months postoperatively, and P_c denotes the proportion of the randomized control group reaching the same endpoint.

Seventy-four out of 116 subjects (63.79%) in the Treatment Group and 58 out of 123 subjects (47.15%) in the Control Group met this endpoint. This difference of 16.64% produced a p-value of 0.0133 using a 2-sided Fisher's exact test.

Effects of Missing Data:
In order to assess the effects of missing data, we present Table 34. The Non-Responder analysis assumes that those who were missing at 12 months are all failures, regardless of their assigned study arms. The Complete-Case Analysis includes all subjects with no missing data. It was found that both Complete-Case and Non-Responder analyses provided statistically significant p-value of 0.0133 while the Worst-Case analysis yielded an insignificant p-value of 0.2375.

As was done for the primary endpoint, FDA conducted a Tipping-Point analysis and obtained similar findings. The results are shown in Table 35.

"As Treated" Analyses:
Table 36 shows the results of the As-Treated (AT) analyses. The results are similar to those of the "analyses based upon randomization," except that the worst-case analysis yielded a significant p-value (p=0.0323), as for the primary effectiveness endpoint.

Results at 24 Months Postop:
Table 37 presents the results for the secondary effectiveness endpoint at 24 months using "analyses based upon randomization" and AT analyses, respectively. Again, none of the tests are statistically significant.

Neither the primary nor the secondary effectiveness endpoints have been met at the 24-month visit, with either the "analyses based upon randomization," or the AT analyses.

Given that the time point for evaluation of the primary and secondary effectiveness endpoint was pre-specified in the protocol as 12 months postoperatively, the panel members will be asked if the lack of statistical significance between the randomized arms for these endpoints at 24 months postoperatively modifies their risk/benefit assessment for this device.

6.2.10.2.4 Timing of Re-Introduction of Anti-Hypertensive Medications

Evidence Concerning Possible Bias

Re-introduction of intraocular pressure (IOP)-lowering medications post-operatively was at the investigators' discretion. The lack of standardized criteria for re-introducing IOP-lowering medications and the lack of masking raised concerns as to whether there were differences between the two randomized study arms with regard to the IOP at which medications were re-introduced.

FDA evaluated whether the timing of the re-introduction of medication may have affected the primary and secondary effectiveness outcomes, by looking at the last available non-medicated IOPs in subjects who were "rescued" through reintroduced to anti-hypertensive medication.

In the randomized study:

- For Controls: There were 41 rescued subjects.
  - 11 of these had final unmedicated IOPs ≤ 21, and
  - 9 had final unmedicated IOPs with ≥ 20% reduction from unmedicated baseline.

- For the Treatment group (iStent): There were 18 rescued subjects.
  - 2 of these had final unmedicated IOPs ≤ 21, and
  - 2 had final unmedicated IOPs with ≥ 20% reduction from unmedicated baseline.

FDA analysis indicates that these differences would not have affected the statistical significance of the main effectiveness outcomes. They may have affected the magnitude of the differences between the success rates of the two randomized groups.

The applicant submitted a table containing summary data concerning the last non-medicated IOPs for the rescued subjects. The mean IOP at which the medications were re-introduced in the Treatment Group and the Control Group were 30.1 mmHg and 28.4 mmHg, respectively. (Table 10 shows this summary data, and the FDA-generated p-value of 0.5394, indicating the difference of these mean IOPs between the two randomized groups is not statistically significant.)

There were no standardized criteria for the re-introducing "rescue" IOP-lowering medications in the pivotal study. Given the observed differences between the two randomized study arms in terms of how "rescue" medications were re-introduced, the panel members will be asked to provide their opinions concerning how significantly, if at all, these affected effectiveness outcomes.

6.2.10.2.5 Other Analyses (Requested or Performed by FDA)

The following additional analyses have been performed at FDA's request or by FDA to further clarify device effectiveness.

Measures of IOP Central Tendency (Descriptive Statistics) – Last Available Non-Medicated IOP for Subjects Available at 12 Months.

Due to the fact that some patients had anti-hypertensive medications re-introduced after surgery, it is difficult to get an unbiased measure of the effect of the stent on IOP.

In order to get some sense for how IOP was affected by the study treatments in the randomized groups, FDA looked at the mean and median last non-medicated IOPs for all completed eyes.

Last available non-medicated IOP (completed subjects):

- Control Group: Mean = 21.1 mmHg; Median = 18 mmHg;
- iStent Group: Mean = 19.2 mmHg; Median = 17.5 mmHg.

For purposes of comparison, we provide the mean and median non-medicated baseline IOPs for completed subjects:

- Control Group: Mean = 25.5 mmHg; Median = 24 mmHg;
- iStent Group: Mean = 25.5 mmHg; Median = 24.25 mmHg.

In subjects who were "rescued" with medication before 12 months postop, their last available non-medicated IOPs are likely to underestimate the "true" IOP at 12 months. FDA believes that this underestimation is less likely to substantially affect the median than the mean. (This is because most "rescued" subjects had high IOPs when rescued.)

Combined Endpoints

The applicant was asked to conduct analyses of combined endpoints as follows:

a. Please report the percentage of subjects (eyes) in each group that meet all of the following criteria:
   i. IOP > 6 mmHg
   ii. On no IOP-lowering medications
   iii. Less than a 2-line letter decrease (< 10 letters on an ETDRS chart) in BCVA from baseline
   iv. Experience no adverse events
   v. Decrease in IOP from baseline by at least 20%

b. Please report the percentage of subjects in each group that meet the first 4 criteria and the following criteria:
   i. At least 15% reduction in IOP from baseline, if the baseline IOP is < 24 mmHg
   ii. At least 20% reduction in IOP from baseline, if the baseline IOP is 25-29 mmHg
   iii. At least 30% reduction from baseline, if the baseline IOP is > 30 mmHg

c. Please report the percentage of subjects in each group that meet the first 4 criteria in part (a) and the following criterion: decrease in IOP from baseline by > 3 mmHg.

The analyses are summarized in Table 38 (non-responder analysis, based upon randomization). Instead of p-values, the sponsor presented 90% Confidence Intervals for all comparisons of outcomes. 90% Confidence Intervals were used because the corresponding endpoints were tested with a one-sided significance level of 0.05. It was discovered that the difference between the

randomized Treatment Group and the randomized Control Group in 12-month data is larger than those in the 24-month data. This finding is consistent through all analysis populations for similar comparisons of effectiveness outcomes.

The panel will be asked which of the additional analyses that were performed at FDA's request, if any, should be included in device labeling.

Effectiveness Outcomes of Subjects with Pseudoexfoliative or Pigmentary Glaucoma vs. Outcomes of Other Subjects

FDA was concerned that subjects with pseudoexfoliative glaucoma and subjects with pigmentary glaucoma would have different outcomes than those of the rest of the cohort. Therefore, the applicant was asked to perform analyses to address this issue. Table 39 shows these analyses (for the non-responder analyses based upon randomization).

It appears that the subpopulation of subjects with Pigmentary or Pseudoexfoliative Glaucoma has generally lower success (response) rates than the group of Other Open Angle Glaucoma for both the Treatment Group and Control Group. It should be pointed out that (1) this analysis does not have sufficient statistical power to detect a true difference; and (2) there are very few cases in the Group of Pigmentary or Pseudoexfoliative Glaucoma. Therefore, no meaningful statistical inference may be drawn from the analyses.

6.2.10.2.6 Site Effects

There were 27 sites participating in the randomized portion of the study. The enrollment by sites is listed in Table 40.

To address the issue of enrollment balance across sites, the study protocol specified that each site "will be asked to enroll 10 subjects to each study arm and no more than 25% of the total subjects in the investigation." According to the data provided by the applicant, only 4 sites (Sites 03, 18, 38 and 47) met this enrollment requirement. In addition, 17 sites had enrollment less than 10 (two randomized arms combined).

The applicant then performed a poolability analysis by grouping sites with small enrollments (shown in Table 41). The bold numbers in parentheses indicate the total enrollment number at each site. A Gail-Simon test of qualitative interaction between study site and treatment groups was conducted at a two-sided level of 0.15 and produced a p-value of 0.984 indicating there was no significant interaction between site and treatment.

FDA noted that the four sites that had the greatest enrollment (Sites #3, #18, #38 and #47) enrolled 104 subjects, 43.3% of the total enrollment. One concern was whether the four largest sites were the driving force of the positive study results. Site size was treated as a binary variable with 1 being assigned to each of the 4 sites with the greatest enrollment and 0 being assigned to each of the other sites. A regression model was run to examine the interaction effect between treatment and site size. A significant p-value of the interaction term may indicate a qualitative difference between large and small sites in terms of device effectiveness. Table 42 lists the results for each effectiveness endpoint. None of the tests has p-value less than 0.15, meaning no

significant interaction effect between treatment and site, i.e., no significant evidence that the four largest sites might have driven the study.

The data in Table 42 indicated that none of the interaction term was statistically significant for all effectiveness endpoints of interest, which implies that there is no significant evidence that the four largest sites drove the study.

The non-randomized population consisted of 50 subjects enrolled in the study at 10 sites subsequent to the completion of enrollment of the randomized study population. One of these sites had not enrolled any subjects into the randomized portion of the study. One site enrolled 40% of the non-randomized subjects (35% of the non-randomized subjects that received the iStent). This is the same site that enrolled the most randomized subjects. This site enrolled a total of 55 out of 290 (19%) subjects in the entire study cohort. Six sites enrolled less than 4 subjects. Therefore, a large proportion of the non-randomized subjects that were added to be included in the safety population were enrolled by the surgeon with the most experience with the device.

Given the unequal distribution of subjects across study sites, the panel members will be asked whether they believe the data presented is sufficient to support the effectiveness of the device.

7 Post-Approval Studies

NOTE TO PANELISTS: FDA's inclusion of a section/discussion on a Post-Approval study (PAS) in this executive summary should not be interpreted to mean that FDA has made a decision on the approvability of this PMA. The presence of post-approval study plans or commitments does not in any way alter the requirements for premarket approval. A recommendation from the Panel on whether the data demonstrates reasonable assurance on device safety and effectiveness must be based solely on the premarket data. The issues noted below are FDA's comments regarding potential post-approval studies.

Overview of Proposed Post-Approval Studies

FDA worked interactively with the Glaukos Corporation to develop the post-approval study protocols. There are two post-approval studies proposed: one for the existing PMA cohort (I) and one for a newly enrolled cohort (II).

7.1 Post-Approval Study I

7.1.1 Study Objectives

To assess the long-term safety of the Glaukos iStent Trabecular Micro-Bypass Stent Model GTS100R/L in subjects previously enrolled in Glaukos Study GC-003.

7.1.2 Study Design and Hypotheses

This is an extended follow-up study of subjects previously enrolled in Glaukos Study GC-003.

7.1.3 Population and Sample Size

Among the 290 subjects (with 290 qualified eyes) enrolled in Study GC-003, extended follow-up is planned on subjects eligible to participate in this extended follow-up study. Subjects will be followed for five years postoperatively.

7.1.4 Data collection (Endpoints)

7.1.4.1 Safety Measurement

The intra-operative and post-operative ocular adverse events will be collected. The sight-threatening adverse events include BCVA loss >3 lines, endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment, and aqueous misdirection. Other important ocular adverse events include increase in IOP of >10 mmHg at any time postoperative, and loss of best spectacle corrected visual acuity of > 1 line (> 5 letters) at >3 months postoperative.

7.1.4.2 Other Clinical Parameters

- Manifest refraction
- Best Corrected VA (Snellen) with BAT
- Best Spectacle Corrected VA (ETDRS)
- IOP via Applanation Tonometry
- Gonioscopy
- Fundus exam/nerve abnormality assessment
- Vertical C/D ratio
- Visual field
- Pachymetry
- Complications and adverse events
- Device failures

7.1.5 Follow-up Visits and Length of Follow-up

All subjects will participate in scheduled follow-up visits over the course of 5 years postoperative. A corresponding case report form will be completed for each scheduled exam. Data from unscheduled or interim visits will also be recorded using appropriate case report forms. Subjects will be examined and evaluated according to the following schedule:

- Visit 1- Month 36 Postoperative (±45 days)
- Visit 2- Month 42 Postoperative (±45 days)
- Visit 3- Month 48 Postoperative (±45 days)
- Visit 4- Month 54 Postoperative (±45 days)
- Visit 5- Month 60 Postoperative (±45 days)

7.2 Post-Approval Study II

7.2.1 Study Objectives

To assess the long-term safety of the Glaukos iStent® Trabecular Micro-Bypass Stent Model GTS100R/L in conjunction with cataract surgery compared to cataract surgery only, in subjects with mild to moderate open-angle glaucoma.

7.2.2 Study Design and Hypotheses

- Prospective, randomized, concurrently controlled, parallel group, multicenter investigation
- Surgery consisting of implantation of one GTS100 stent in conjunction with cataract surgery (treatment group), or cataract surgery only (control group)
- 1:1 randomization plan (treatment group to control group)
- Follow-up through 5 years postoperatively

The goal of this study is to demonstrate that within 5 years of implantation the device in conjunction with cataract surgery does not result in a rate of sight-threatening adverse events that is higher than the rate of sight-threatening adverse events that occurs after cataract surgery alone, by more than a non-inferiority margin of 5%.

The null hypothesis (HO) is that the rate of sight-threatening adverse events in the treatment group (P_T) is at least 5% greater than the rate in the control group (P_C).

The alternative hypothesis (HA) is that the rate of sight-threatening adverse events in the treatment group is less than 5% greater than that in the control group, as follows:

$$H_O: P_T - Pc \geq 5\%$$
$$H_A: P_T - Pc < 5\%$$

7.2.3 Population and Sample Size

PAS II: A total of 360 qualified eyes of 360 subjects (one per subject) with mild to moderate open-angle glaucoma will be randomized in the study (180 eyes in Group 1, 180 eyes in Group 2) at up to 45 clinical sites. It is expected that at least 1100 subjects will undergo screening and baseline exams, and/or operative procedures in order to obtain 360 randomized subjects.

The rate of sight-threatening adverse events was estimated from the Glaukos Clinical Trial Study #GC-003 (A Study of the Glaukos™ Trabecular Micro-Bypass Stent in Combination with Cataract Surgery in Open-Angle Glaucoma Subjects). In the---------- IDE progress report (March, 2010), the 2-year rate of sight threatening adverse events (including BCVA loss ≥3 lines, endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment and aqueous misdirection) of stent treated subjects was 1% (1/111) as compared to 2% (21122) in the control group.

With estimated rates of 0.03 (3%) for P_T and P_C at 5 years, a Type I error rate of 10%, a Type II error rate of 20% (i.e., 80% power), a randomization ratio of 1:1, 1-sided testing, a two-group large-sample normal approximation test of proportions, and a δ of 0.05 (i.e., a non-inferiority margin of 0.05 or 5%), the required sample size is 212 subjects (or 106 per group). The sample size is derived per ISO 15798:2010. With allowance for up to 10% losses per year (for 5 years) to follow-up, the sample size for enrollment is set at 360 subjects, of whom 180 will undergo stent implantation in conjunction with cataract surgery and 180 will undergo cataract surgery only.

7.2.4 Data collection (Endpoints)

7.2.4.1 Safety Measurement

The intraoperative and postoperative ocular adverse events will be collected. The sight-threatening adverse events include BCVA loss ≥3 lines, endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment, and aqueous misdirection. Other important ocular adverse events include increase in IOP of ≥10 mmHg at any time postoperative, and loss of best spectacle corrected visual acuity of ≥1 line (≥5 letters) at ≥3 months postoperative.

7.2.4.2 Other Clinical Parameters:

- Manifest refraction
- Best Corrected VA (Snellen) with BAT
- Best Spectacle Corrected VA (ETDRS)
- Pinhole VA
- Slit lamp exam
- IOP via Applanation Tonometry
- Diurnal IOP via Applanation Tonometry (8:00 am, 12:00 pm, and 4:00 pm)
- Gonioscopy
- Fundus exam/nerve abnormality assessment
- Vertical C/D ratio
- Visual field
- Pachymetry
- Subjective assessment
- Complications and adverse events
- Device failures

7.2.5 Follow-up Visits and Length of Follow-up

7.2.5.1 PAS I

All subjects will participate in scheduled follow-up visits over the course of 5 years postoperative. A corresponding case report form will be completed for each scheduled exam. Data from unscheduled or interim visits will also be recorded using appropriate case report forms. Subjects will be examined and evaluated according to the following schedule:

- Visit 1- Month 36 Postoperative (±45 days)
- Visit 2- Month 42 Postoperative (±45 days)
- Visit 3- Month 48 Postoperative (±45 days)
- Visit 4- Month 54 Postoperative (±45 days)
- Visit 5- Month 60 Postoperative (±45 days)

7.2.5.2 PAS II

Preoperative screening evaluation (day -60 to day -5)

- Baseline evaluation (after completion of appropriate medication washout period
- Day 0: iStent implantation
- Postoperative 2 to 10 hours
- 1-2 Days
- 1-2 Weeks (7-14 days)
- 1 Month (±1 week)
- 3 Months (±2 weeks)
- 6 Months (±30 days)
- 12 Months (±30 days)
- 18 Months (±45 days)
- 24 Months (±45 days)
- 30 Months (±45 days)
- 36 Months (±45 days)
- 42 Months (±45 days)

- 48 Months (±45 days)
- 54 Months (±45 days)
- 60 Months (±45 days)

7.3 FDA Comments on the Post-Approval Studies:

- The proposed post-approval study protocols are the result of interactive review efforts involving FDA and Glaukos Corporation. The applicant initially proposed only to extend the follow-up of the PMA cohort. FDA recommended adding the new patient cohort for a 5-year follow-up and the applicant agreed. FDA also recommended using a concurrent cohort for comparison; adding diurnal IOP measurement to adjust the diurnal fluctuation of IOP; making it consistent in the site training and education; specifying the detailed adverse events possible to happen post-operatively, and the applicant has satisfactorily completed the recommended updates.

- However, for the post-approval study with new patients, the applicant proposed a sample size of 180 eyes (one eye per patient) each for the treatment group and the control group. The applicant has chosen a non-inferiority margin of 5% for severe adverse events. The AE rates in the PMA study were 1% for the treatment group and 2% for the control group. The appropriateness of the non-inferiority margin still needs to be determined. FDA continues to work interactively with the applicant to reach agreement on the protocol details.

7.4 Issues for Panel Consideration:

- ***Should the system be approved, the applicant has proposed a three-year continuation of the existing PMA study GC-003 as one of the post-approval studies, as well as a newly enrolled, prospective, randomized, concurrently controlled, parallel group of 360 patients from multicenter location. The Panel will be asked to comment on the adequacy and appropriateness of the study designs, endpoints, potential adverse events and length of follow-up of these two studies***.

- ***For the new enrollment study, the applicant has chosen a non-inferiority margin of 5% for the sight-threatening adverse events. The Panel will be asked to on the appropriateness of this assumption***.

FDA Executive Summary
Reference Booklet

Prepared for the
July 30, 2010 meeting of the
Ophthalmic Devices Panel

P080030
Glaukos, Inc.
iStent Trabecular Micro-Bypass Stent
Model GTS-100 R/L

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Figure 1: Implant

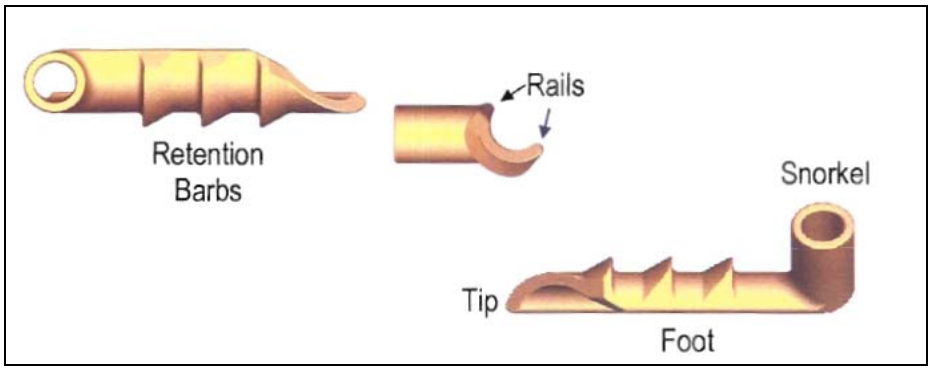


Figure 2: Inserter

Figure 3: Procedure

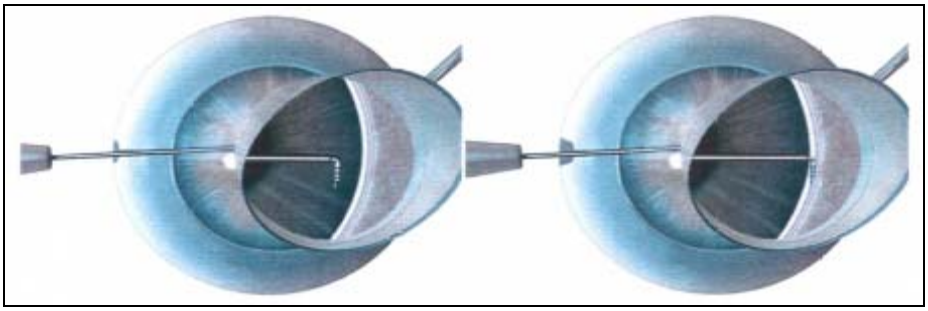


Figure 4: GC003 Study Flow Chart

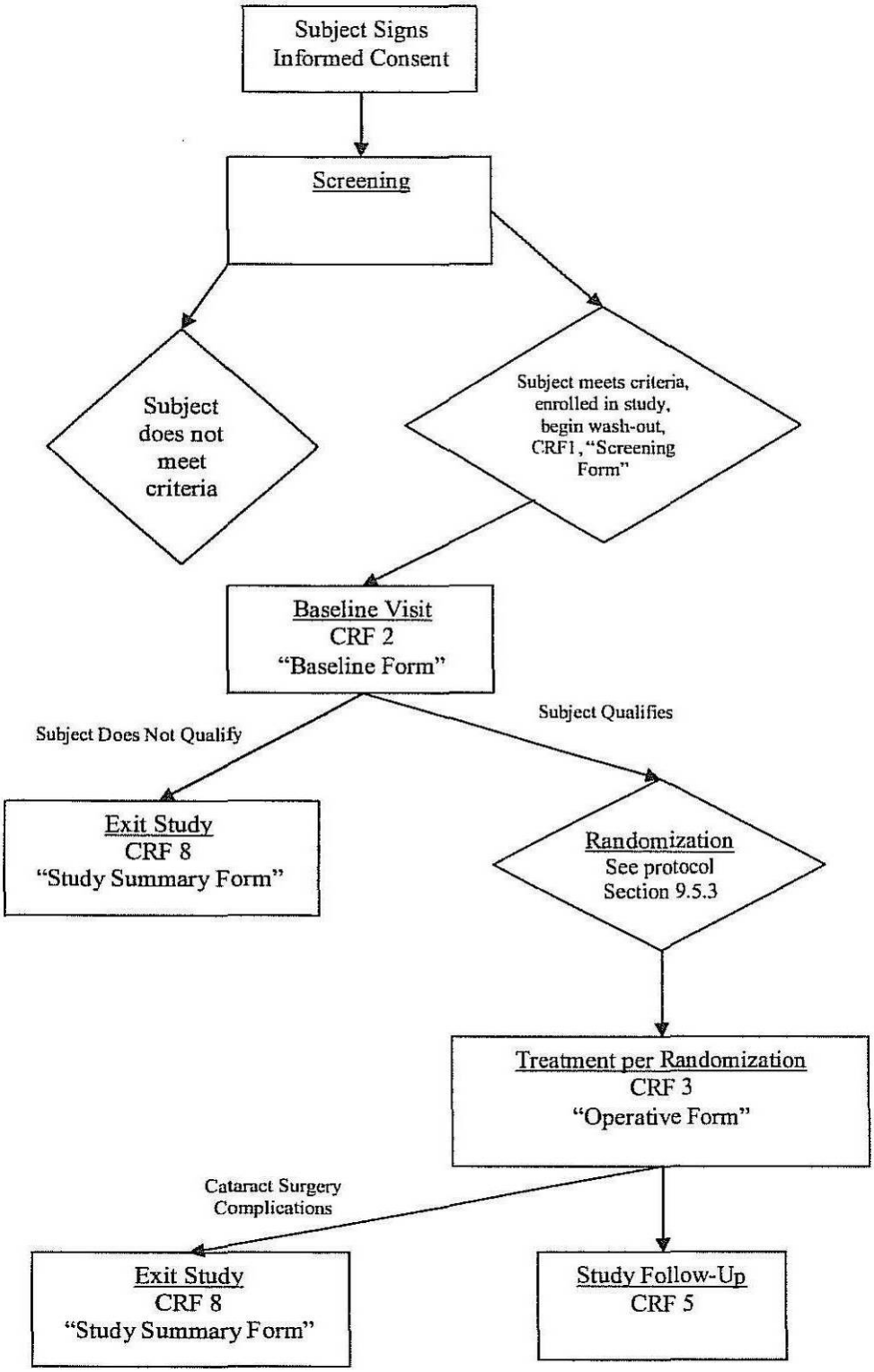
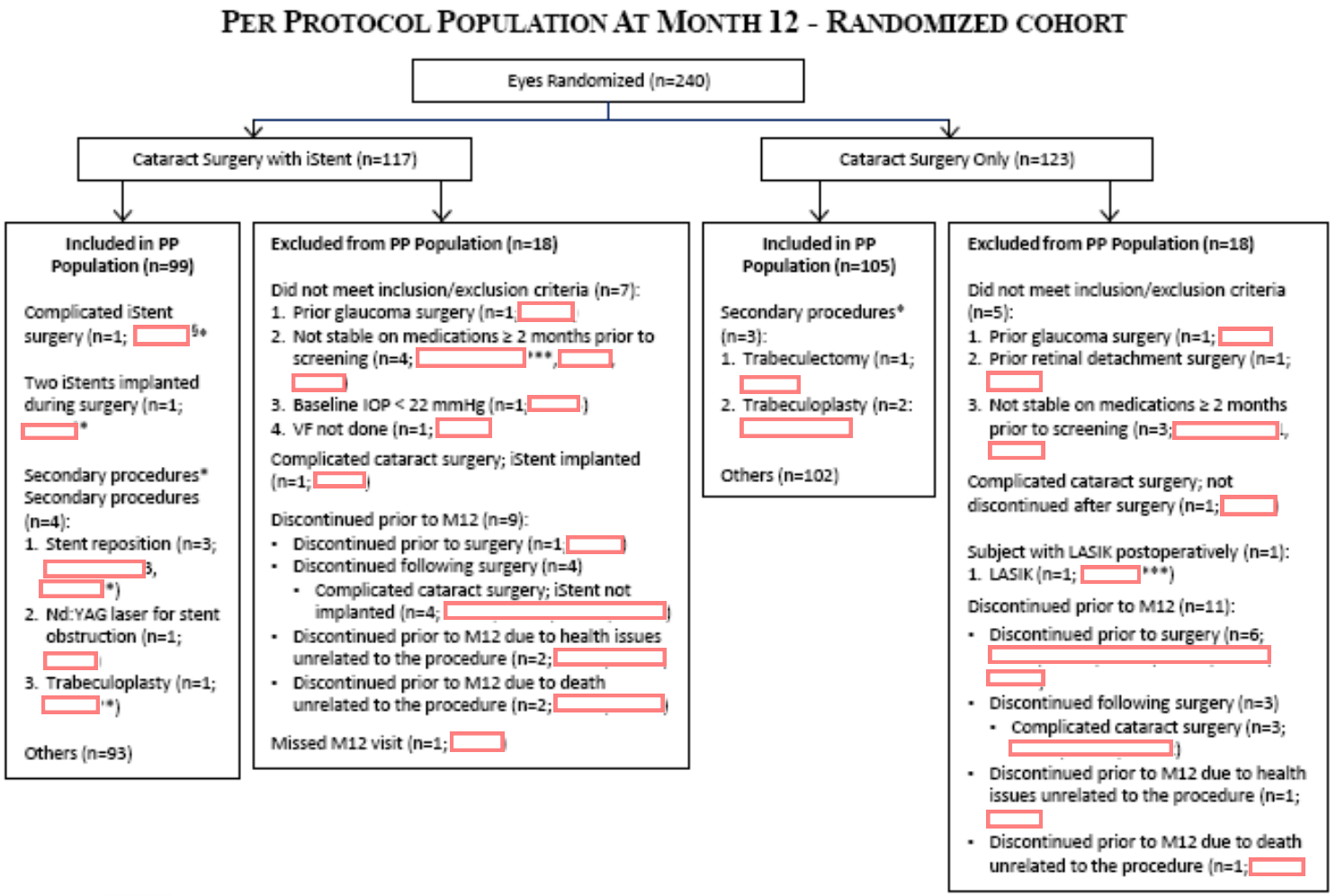


Figure 5: Intent to Treat Population (All Randomized Subjects)

(subjects randomized in the study, regardless of whether they received the randomly assigned study treatment (with or without iStent))

** Three subjects exited immediately after cataract surgery; 1 subject exited several weeks after cataract surgery following postoperative resolution of the operative complication (subluxation of crystalline lens treated with vitrectomy)*

Figure 6: Per Protocol Population at Month 12 - Randomized Cohort



§Although subject discontinued following surgery and does not have M12 data, they are included in per protocol population and considered a non-responder per FDA request

*subjects to be considered non-responders for relevant efficacy analyses

**same eye

***although subject had a secondary surgical procedure, they are excluded from per protocol population since they did not meet inclusion/exclusion criteria

****although subject had a secondary surgical procedure, they are excluded from per protocol population per FDA request

Table 1: iStent Biocompatibility Testing

Test Description	Sample testing	Results	Applicable Standards
Cytotoxicity (inhibition of cell growth, 9-point assay)	Heparin-coated Titanium discs (sterile)	Cell growth inhibition <10%	N/A (NAMSA test method)
Cytoxicity (ISO MEM Elution)	Heparin Coated Titanium stents (Sterile)	No cell lysis or toxicity	ISO 10993-5
Genotoxicity (Bacterial Reverse Mutation)	Heparin Coated Titanium stents (Sterile)	No mutagenic changes	ISO 10993-3
Mouse Bone Marrow Micronucleus Study	Heparin Coated Titanium stents (Sterile)	No toxicity of mutagenic effects	OECD Guideline 474
In Vitro Chromosomal Aberration Study	Heparin Coated Titanium stents (Sterile)	No chromosomal aberrations induced	OECD Guideline 473
Intraocular Irritation study in the Rabbit	Heparin Coated Titanium discs (Sterile)	No evidence of irritation	N/A (NAMSA test method)
ISO Maximization Sensitization Study	Heparin Coated Titanium stents (Sterile)	No evidence of delayed dermal contact sensitization	ISO 10993-10
Muscle Implantation in the Rabbit	Heparin Coated Titanium discs (Sterile)	Macroscopic reaction not significant; non irritant	ISO 10993-6
Acute Toxicity in Mouse	Heparin Coated Titanium stents (Sterile)	No mortality or evidence of systemic toxicity	ISO 10993-11
USP Pyrogen Study-material mediated	Heparin Coated Titanium stents (Sterile)	Temperature rise within acceptable USP limits	ISO 10993-11
Histopathological Evaluation of Cadaver Tissue	Heparin Coated Titanium stents (Sterile)	No Morphologic Alterations of tissue, and very little evidence of physical trauma to the tissues examined	N/A

Table 2: Activities Conducted During Clinical Study

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

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

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

Table 3: Follow-up Examination Schedule

Follow-up Evaluation	Acceptable Time Interval (Days from Operative Evaluation)
5 hours	5 hours ± 2 hours post-op
1 day post-op	1 day post-op
7-14 days post-op	7-14 days post-op
1 month post-op	30 days ± 10 days
3 months post-op	90 days ± 25 days
6 months post-op	180 days ± 30 days
12 months post-op	360 days ± 45 days
18 months post-op	540 days ± 60 days
24 months post-op	720 days ± 75 days

Table 4: Demographics and Baseline Characteristics (created by FDA)

	Randomized Group		Non-Randomized Group	Total	P-value[1]	P-value[2]
	Cataract Surgery with iStent® n=116	Cataract Surgery Only n=123	Cataract Surgery with iStent® n=50	N=289		
Age (Years)						
N	116	123	50	289	0.3088	0.7185
Mean	73.96	72.88	73.49	73.42		
Std. Dev.	7.66	8.66	7.79	8.11		
Minimum	53.39	48.92	54.93	48.92		
Maximum	88.57	88.52	87.52	88.57		
<60	4 (3.45%)	12 (9.76%)	3 (6.00%)	19 (6.57%)	0.2431	0.4845
60 to <70	33 (28.45%)	31 (25.20%)	10 (20.00%)	74 (25.61%)		
70 to <80	49 (42.24%)	53 (43.09%)	26 (52.00%)	128 (44.29%)		
≥80	30 (25.86%)	27 (21.95%)	11 (22.00%)	68 (23.53%)		
Gender						
Male	46 (39.66%)	52 (42.28%)	19 (38.00%)	117 (40.48%)	0.6951	0.8643
Female	70 (60.34%)	71 (57.72%)	31 (62.00%)	172 (59.52%)		
Race						
American Indian or Alaska Native	1 (0.86%)	1 (0.81%)	0 (0%)	2 (0.69%)	0.7747	0.0904
Asian	1 (0.86%)	0 (0%)	1 (2.00%)	2 (0.69%)		
Black or African American	15 (12.93%)	19 (15.45%)	3 (6.00%)	37 (12.80%)		
Native Hawaiian or Pacific Islander	1 (0.86%)	0 (0%)	0 (0%)	1 (0.35%)		
Hispanic or Latino	16 (13.79%)	15 (12.20%)	16 (32.00%)	47 (16.26%)		
White	82 (70.69%)	88 (71.54%)	30 (60.00%)	200 (69.20%)		
Medicated IOP (mmHg) at Screening						
N	116	123	50	289	0.0885	0.0946
Mean (SD)	18.73 (3.28)	18.04 (3.03)	18.01 (3.24)	18.31 (3.18)		
Min, Max	9.50, 24.00	12.00, 24.00	11.00, 24.00	9.50, 24.00		
Unmedicated IOP (mmHg) at Baseline						
N	116	123	50	289	0.5573	0.6546
Mean (SD)	25.23 (3.46)	25.50 (3.72)	24.98 (2.93)	25.30 (3.49)		
Min, Max	21.00, 36.00	21.50, 36.00	22.00, 35.00	21.00, 36.00		
Subjects using IOP-lowering Medications at Baseline (%)						
One Medication	61	59	67			
Two Medications	24	33	26			
Three medications	15	7	7			

[1]Randomized iStent Group vs. Control Group – Fisher's test for categorical variables, ANOVA for continuous variables

[2]Randomized iStent Group vs. non-Randomized iStent Group – Fisher's test for categorical variables, ANOVA for continuous variables

Table 5: Baseline Parameters (ITT Population)

	Randomized Group		
	Cataract Surgery with iStent® N = 117 n (%)	Cataract Surgery Only N = 123 n (%)	Total N = 240 n (%)
Unmedicated IOP (mmHg)			
N	117	123	240
Mean (SD)	25.2 (3.5)	25.5 (3.7)	25.4 (3.6)
Minimum, Maximum	21, 36	22, 36	21, 36
Unmedicated IOP Measured Time			
AM	93 (79%)	97 (79%)	190 (79%)
PM	24 (21%)	26 (21%)	50 (21%)
Visual Disturbance			
Yes	32 (28%)	35 (29%)	67 (28%)
No	83 (72%)	86 (71%)	169 (72%)
Manifest Refraction Spherical Equivalent (MRSE)			
N	80	85	165
Mean (SD)	-0.430 (2.637)	-0.582 (3.003)	-0.508 (2.824)
Minimum, Maximum	-10.625, 4.750	-9.750, 5.125	-10.625, 5.125
Best Corrected Visual Acuity (LogMAR)			
N	116	121	237
Mean (SD)	0.35 (0.21)	0.36 (0.26)	0.36 (0.23)
Minimum, Maximum	-0.10, 1.00	-0.16, 1.74	-0.16, 1.74
Visual Field, Mean Deviation (MD)			
N	115	121	236
Mean (SD)	-3.75 (3.03)	-3.74 (3.86)	-3.74 (3.47)
Minimum, Maximum	-14.2, 3.25	-16.3, 12.72	-16.3, 12.72
Visual Field, Pattern Standard Deviation (PSD)			
N	110	112	222
Mean (SD)	2.89 (1.79)	2.79 (1.90)	2.84 (1.85)
Minimum, Maximum	1.15, 11.20	1.10, 10.38	1.10, 11.20
Pachymetry (µm)			
N	117	123	240
Mean (SD)	550 (43)	548 (37)	549 (40)
Minimum, Maximum	403, 735	462, 642	403, 735
Diagnosis			
Pigmentary Glaucoma	4 (3%)	3 (2%)	7 (3%)
Pseudoexfoliative Glaucoma	7 (6%)	7 (6%)	14 (6%)

IOP = Intraocular pressure. Median IOP of multiple measurement was calculated for each eye and it was treated as the IOP measurement for the eye.

Table 6: Baseline Parameters (Non-Randomized Group)

	Cataract Surgery with iStent® N = 46 n (%)
Unmedicated IOP (mmHg)	
n	46
Mean (SD)	24.9 (3.0)
Minimum, Maximum	22, 35
Unmedicated IOP Measured Time	
AM	34 (74%)
PM	12 (26%)
Visual Disturbance	
Yes	20 (43%)
No	26 (57%)
Manifest Refraction Spherical Equivalent (MRSE)	
n	45
Mean (SD)	-0.958 (3.037)
Minimum, Maximum	-14.750, 3.250
Best Corrected Visual Acuity (LogMAR)	
n	45
Mean (SD)	0.35 (0.26)
Minimum, Maximum	0.06, 1.60
Visual Field, Mean Deviation (MD)	
n	45
Mean (SD)	-3.79 (3.92)
Minimum, Maximum	-18.5, 0.28
Visual Field, Pattern Standard Deviation (PSD)	
n	46
Mean (SD)	2.48 (1.61)
Minimum, Maximum	1.13, 10.23
Pachymetry (µm)	
n	46
Mean (SD)	547 (43)
Minimum, Maximum	433, 688
Diagnosis	
Pigmentary Glaucoma	0 (0%)
Pseudoexfoliative Glaucoma	0 (0%)

IOP = Intraocular pressure. Median IOP of multiple measurements was calculated for each eye and it was treated as the IOP measurement for the eye.

Table 7: Cumulative Summary of Protocol Deviations - Randomized Cohort

DEVIATIONS	Cataract Surgery with iStent®	Cataract Surgery Only
ELIGIBILITY DEVIATIONS		
Prior glaucoma surgery	1	1
Previous retinal detachment surgery	0	1
Randomization envelope opened out of sequence	3	3
Not stable on hypotensive medications for ≥2 months	4	3
Fellow eye enrolled in study	1	0
Fellow eye not 20/200 or better; measurement not done at screening	3	0
Baseline IOP <22 or >36	1	0
Visual field examination requirement not met	1	0
INFORMED CONSENT FORM •10 subjects missing California Bill of Rights (9 signed; 1 deceased) •4 subjects signed the ICF after the Screening visit but prior to surgery •2 subjects signed improper version of ICF; have signed correct version	7 5 1 1	8 5 2 1
INTRAOPERATIVE DEVIATIONS		
iStent® implanted was past expiration date	1	0
Accommodative IOLs implanted rather than standard IOLs	1	2
Limbal versus clear corneal incision used	7	8
Dispersive versus cohesive viscoelastics used	1	7
Stent implanted in subject following complications of cataract surgery vs. exited from study	1	0
Subject continued in study following complications of cataract surgery vs. exited from study	0	1
VISIT AND ASSESSMENT DEVIATIONS		
ETDRS Visual Acuity •Not performed at Baseline (2 deviations, 2 subjects) •Not performed at one or more visits (33 deviations, 25 subjects)	16 1 15	19 1 18
IOP measurement at 5 hours (±2) postoperative made out of time window (minimum measurement taken at 2.4 hours; not reported for one subject)	1	3
Pachymetry not performed at scheduled visit	4	3
Gonioscopy not performed at one or more scheduled visits	30	N/A
Manifest refraction not performed at one or more scheduled visits	23	21
Slit lamp examination not performed at one or more scheduled visits	0	1
Fundus examination not performed at scheduled visit	8	2
Visual Field examination not performed at one or more scheduled visits	5	4
Visual Field algorithm different from protocol requirement	6	3
CD ratio measurement not performed at scheduled visit	3	2
Follow-up visits (one or more) performed outside of visit window 1 day (n=1); 1-2 weeks (n=17); 1 month (n=9); 3 months (n=6); 6 months (n=6); 12 months (n=0); 18 months (n=5); 24 months (n=3)	19	28

NOTE: ICF = Informed Consent Form; CD = cup-to-disc; IOL = Intraocular Lens

Table 8: Cumulative Summary of Protocol Deviations - Non-Randomized Population

DEVIATIONS	Number of Deviations	Number of Subjects
ELIGIBILITY DEVIATIONS	0	0
INFORMED CONSENT FORM •5 subjects missing California Bill of Rights (5 signed)	5	5
INTRAOPERATIVE DEVIATIONS		
Accommodative IOLs implanted rather than standard IOLs	1	1
Limbal versus clear corneal incision used	2	2
VISIT AND ASSESSMENT DEVIATIONS		
ETDRS Visual Acuity •Not performed at Baseline (1 deviation, 1 subject) •Not performed at one or more* visits (4 deviations, 3 subjects)	5 1 4	4 1 3
IOP measurement at 5 hours (±2) postoperative made out of time window (minimum measurement taken at 2.4 hours; not reported for one subject)	2	2
Pachymetry not performed at scheduled visit	1	1
Gonioscopy not performed at one or more* scheduled visits	1	1
Manifest refraction not performed at one or more* scheduled visits	4	3
Slit lamp examination not performed at one or more* scheduled visits	2	1
Visual Field examination not performed at one or more* scheduled visits	1	1
Visual Field algorithm different from protocol requirement	1	1
Follow-up visits (one or more*) performed outside of visit window 1 day (n=0); 1-2 weeks (n=3); 1 month (n=0); 3 months (n=1); 6 months (n=3); 12 months (n=1); 18 months (n=0); 24 months (n=0)	8	6

Table 9: Records Out of Visit Windows - Non-Randomized Population

Site #	Subject ID	Actual Treatment	Visit	Visit Date	Day from Surg	Day from Window	IOP	IOP Change	IOP % Change	Anti-Glaucoma Medications at the Begining of Visit
Non-Randomized Treatment: Non-randomized Cataract Surgery with iStent (N = 6)										
25	[redacted]	Non-randomized Cataract Surgery with iStent	1-2 Weeks	07/24/07	6	-1	18.0	-5.5	-23.4	
43	[redacted]	Non-randomized Cataract Surgery with iStent	6 Months	07/18/08	255	45	14.0	-9.8	-41.1	Azopt, Alphagan
46	[redacted]	Non-randomized Cataract Surgery with iStent	1-2 Weeks	01/18/08	15	1	28.0	-4.0	-12.5	
			12 Months	11/10/08	312	-3	16.5	-15.5	-48.4	
47	[redacted]	Non-randomized Cataract Surgery with iStent	6 Months	05/02/08	226	16	14.5	-7.5	-34.1	
47	[redacted]	Non-randomized Cataract Surgery with iStent	3 Months	01/28/08	138	23	13.0	-13.0	-50.0	
			6 Months	04/15/08	216	6	15.5	-10.5	-40.4	
47	[redacted]	Non-randomized Cataract Surgery with iStent	1-2 Weeks	02/19/08	6	-1	16.0	-6.0	-27.3	

Table 10: Comparison of Last IOP prior to Medication (lasting to Month 12) (conducted by FDA)

	Treatment Group (n=18)	Control Group (n=41)	p-value
(min, max)	(19.5, 48.75)	(13, 59.5)	
mean ± std	30.07 ± 8.56	28.35 ± 10.32	0.5394
median	29.00	25.5	

Table 11: Secondary Surgical Interventions - Adverse Events - Safety Population

SAFETY POPULATION

Secondary Surgical Intervention[1] Adverse Events	Randomized Group		Non-Randomized
	Cataract Surgery with iStent® N = 116 n (%)	Cataract Surgery Only N = 117 n (%)	Cataract Surgery with iStent® N = 46 n (%)
Paracentesis[2,3]	31 (27%)	34 (29%)	12 (26%)
Nd:YAG laser capsulotomy[4]	7 (6%)	11 (9%)	7 (15%)
Stent repositioning[3]	3 (3%)	0 (0%)	0 (0%)
Punctal cautery/punctual plugs[3]	1 (1%)	3 (3%)	0 (0%)
Trabeculoplasty[3]	1 (1%)	2 (2%)	0 (0%)
Nd:YAG laser for stent obstruction[3]	1 (1%)	0 (0%)	1 (2%)
Focal argon laser photocoagulation[3]	1 (1%)	0 (0%)	0 (0%)
Stent removal and replacement[3]	1 (1%)	0 (0%)	0 (0%)
Deep sclerectomy/sclerostomy[3]	0 (0%)	1 (1%)	0 (0%)
IOL removal and replacement	0 (0%)	1 (1%)	0 (0%)
LASIK[3]	0 (0%)	1 (1%)	0 (0%)
Pupilloplasty	0 (0%)	1 (1%)	0 (0%)
Vitrectomy	0 (0%)	1 (1%)	0 (0%)
Wound resuture due to wound leak	0 (0%)	1 (1%)	0 (0%)
Iris reposition	0 (0%)	0 (0%)	1 (2%)

Per FDA, treatment for randomized groups was based on randomized assignment. The following eyes were excluded from the analysis due to no surgeries: Randomized iStent: [redacted] Randomized Cataract Only: [redacted], [redacted] and [redacted].

1 Including intervention for elevated IOP

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

3 FDA IOL Guidance Document 1999 defines secondary surgical interventions as secondary surgical procedures that can reasonably be expected to be IOL-related. These surgical interventions are not IOL-related.

4 ISO 11979-7:2006 excludes posterior capsulotomies as secondary surgical interventions for investigations of intraocular lenses.

Table 12: Postoperative Ocular Adverse Events - Safety Population (created by the applicant and modified by FDA)

Adverse Events	Randomized Treatment Group [1] (Cataract Surgery with iStent®) N = 116 n (%)	Randomized Control Group [2] (Cataract Surgery Only) N = 117 n (%)	Non-Randomized Group [3] (Cataract Surgery with iStent®) N = 46 n (%)	Combined Treatment Group [1] + [3] (Cataract Surgery with iStent®) N = 162 n (%)
Anticipated early postoperative event				
Early postop corneal edema	9 (8%)	11 (9%)	2 (4%)	11 (6.8%)
Early postop anterior chamber cells	4 (3%)	2 (2%)	2 (4%)	6 (3.7%)
Early postop corneal abrasion	3 (3%)	2 (2%)	1 (2%)	4 (2.5%)
Early postop corneal striae	2 (2%)	1 (1%)	1 (2%)	3 (1.9%)
Early postop discomfort	1 (1%)	2 (2%)	0 (0%)	1 (0.6%)
Early postop subconjunctival hemorrhage	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Early postop superficial punctate keratitis	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Early postop blurry vision	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Early postop floaters	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Early postop anterior chamber inflammation	0 (0%)	0 (0%)	1 (2%)	1 (0.6%)
Early postop corneal erosion	0 (0%)	0 (0%)	1 (2%)	1 (0.6%)
Early postop pain	0 (0%)	0 (0%)	1 (2%)	1 (0.6%)
Any BCVA loss of at least 1 line at or after the three month visit	**8 (7%)**	**12 (10%)**	**3 (7%)**	**11 (6.8%)**
Posterior capsular opacification	7 (6%)	12 (10%)	4 (9%)	11 (6.8%)
Stent obstruction by iris, vitreous, fibrous overgrowth, fibrin, blood, etc.	**5 (4%)**	**0 (0%)**	**2 (4%)**	**7 (4.3%)**
Blurry vision or visual disturbance	4 (3%)	8 (7%)	2 (4%)	6 (3.7%
Elevated IOP - other	**4 (3%)**	**5 (4%)**	**1 (2%)**	**5 (3.1%)**
Stent malposition	**3 (3%)**	**0 (0%)**	**2 (4%)**	**5 (3.1%)**
Subconjunctival hemorrhage	2 (2%)	2 (2%)	0 (0%)	2 (1.2%)
Epiretinal membrane	2 (2%)	1 (1%)	4 (9%)	6 (3.7%)
Drusen	2 (2%)	0 (0%)	0 (0%)	2 (1.2%)
Iris atrophy	2 (2%)	0 (0%)	0 (0%)	2 (1.2%)
Iritis	1 (1%)	6 (5%)	0 (0%)	1 (0.6%)
Conjunctival irritation due to hypotensive medication	1 (1%)	3 (3%)	0 (0%)	1 (0.6%)
Disc hemorrhage	1 (1%)	3 (3%)	0 (0%)	1 (0.6%)
Elevated IOP requiring treatment with oral or intravenous medications or with surgical intervention	**1 (1%)**	**3 (3%)**	**0 (0%)**	**1 (0.6%)**
Allergic conjunctivitis	1 (1%)	2 (2%)	1 (2%)	2 (1.2%)
Dry eye	1 (1%)	2 (2%)	0 (0%)	1 (0.6%)
Macular edema	**1 (1%)**	**2 (2%)**	**0 (0%)**	**1 (0.6%)**
Cystoid macular edema	**1 (1%)**	**1 (1%)**	**1 (2%)**	**2 (1.2%)**
Worsening of glaucoma	1 (1%)	1 (1%)	1 (2%)	2 (1.2%)
Allergy to cosmetics	1 (1%)	1 (1%)	0 (0%)	1 (0.6%)
Age related macular degeneration	1 (1%)	0 (0%)	1 (2%)	2 (1.2%)
Uveitis	**1 (1%)**	**0 (0%)**	**1 (2%)**	**2 (1.2%)**
Bleeding (vitreous hemorrhage or persistent & non-preexisting hyphema)	**1 (1%)**	**0 (0%)**	**0 (0%)**	**1 (0.6%)**
Blepharospasm	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Corneal edema	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Dysesthesia and/or photophobia	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Endo pigment	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Eye splash injury	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Eyelid bruise due to fall	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)

Adverse Events	Randomized Treatment Group [1] (Cataract Surgery with iStent®) N = 116 n (%)	Randomized Control Group [2] (Cataract Surgery Only) N = 117 n (%)	Non-Randomized Group [3] (Cataract Surgery with iStent®) N = 46 n (%)	Combined Treatment Group [1] + [3] (Cataract Surgery with iStent®) N = 162 n (%)
Metallic particle on iris	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Mild throbbing pain	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Periorbital hematoma due to fall	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Possible bacterial conjunctivitis	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Seasonal allergies	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Subconjunctival hemorrhage secondary to aspirin	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)
Transient hypotony	**1 (1%)**	**0 (0%)**	**0 (0%)**	**1 (0.6%)**
Mild pain	0 (0%)	5 (4%)	0 (0%)	0 (0%)
Posterior vitreous detachment	0 (0%)	4 (3%)	2 (4%)	2 (1.2%)
Foreign body sensation	0 (0%)	4 (3%)	0 (0%)	0 (0%)
Rebound inflammation from tapering steroids	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Blepharoconjunctivitis	0 (0%)	1 (1%)	1 (2%)	1 (0.6%)
Worsening of age related macular degeneration	0 (0%)	1 (1%)	1 (2%)	1 (0.6%)
Anterior chamber + 1 cells (at 1 month) requiring treatment	**0 (0%)**	**1 (1%)**	**0 (0%)**	**0 (0%)**
Burning due to dry eye	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Carotid artery disease	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Choroidal detachment	**0 (0%)**	**1 (1%)**	**0 (0%)**	**0 (0%)**
Choroidal tubercle	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Conjunctivitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Endophthalmitis	**0 (0%)**	**1 (1%)**	**0 (0%)**	**0 (0%)**
Episcleritis	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Intermittent tearing	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Keratitis sicca	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Lesion on eyelid	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Macular hole	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Macular traction	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Poor near vision	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Postoperative refractive error	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Proliferative diabetic retinopathy	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Segmental loss of neuroretinal rim	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Superficial punctate keratitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Wound leak	**0 (0%)**	**1 (1%)**	**0 (0%)**	**0 (0%)**
Blepharitis	0 (0%)	0 (0%)	2 (4%)	2 (1.2%)
Vitreous floaters	0 (0%)	0 (0%)	2 (4%)	2 (1.2%)
Iris incarceration	**0 (0%)**	**0 (0%)**	**1 (2%)**	**1 (0.6%)**
Keratitis	0 (0%)	0 (0%)	1 (2%)	1 (0.6%)
Periorbital swelling	0 (0%)	0 (0%)	1 (2%)	1 (0.6%)
Unwanted eyelid sensation	0 (0%)	0 (0%)	1 (2%)	1 (0.6%)
Vitreous condensations	0 (0%)	0 (0%)	1 (2%)	1 (0.6%)

Per FDA, treatment for randomized groups was based on randomized assignment. The following eyes were excluded from the analysis due to no surgeries: Randomized iStent: [redacted]. Randomized Cataract Only: [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

Table 13: Cumulative and Persistent Adverse Events at 12 Months (Safety Population) (created by the applicant and modified by the FDA to include secondary surgical interventions)

Adverse Events	Randomized Treatment Group Cataract Surgery with iStent ® [1] n (%)	Randomized Control Group Cataract Surgery Only [2] n (%)	Non-Randomized Treatment Group Cataract Surgery with iStent [3] n (%)	Combined Treatment Group [1]+[3] n (%)	SPE Rate[1] (FDA Grid) %
Cumulative[2]	**N = 116**	**N = 117**	**N = 46**	**N = 162**	
Cystoid macular edema	1 (0.9%)	1 (0.9%)	1 (2.2%)	2 (1.2%)	**3.0%**
Hypopyon	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	**0.3%**
Endophthalmitis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0%)	**0.1%**
Lens Dislocation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	**0.1%**
Pupillary Block	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	**0.1%**
Retinal Detachment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	**0.3%**
Secondary Surgical Intervention	5 (4.3%)	5 (4.3%)	2 (4.4%)	7 (4.3%)	**0.8%**
Deep sclerectomy	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0%)	—
IOL removal and replacement	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0%)	—
Iris reposition	0 (0.0%)	0 (0.0%)	1 (2.2%)	1 (0.6%)	—
Pupilloplasty	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0%)	—
Vitrectomy	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0%)	—
Wound resuture due to wound leak	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0%)	—
Stent repositioning	3(3%)	0 (0%)	0 (0%)	3 (1.9%)	--
Stent removal and Replacement	1 (1%)	0 (0%)	0 (0%)	1 (0.6%)	--
Nd:YAG laser for stent obstruction	1 (1%)	0 (0%)	1 (2%)	2 (1.2%)	--
Persistent[3]	**N = 106**	**N = 112**	**N = 44**	**N = 150**	
Corneal Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	**0.3%**
Cystoid Macular Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	**0.5%**
Iritis/Uveitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	**0.3%**
Raised IOP Requiring Treatment[4]	—	—	—	—	**0.4%**

Per FDA, treatment for randomized groups was based on randomized assignment. The following eyes were-------- e----- --- he analysis due to no surgeries: Randomized iStent: -------. Randomized Cataract Only: -------, -------, -------, -------, -------, and --------

% = n ÷ N × 100%.

1. ISO IOL SPE (safety and performance endpoint) rate is the target rate for each event.

2. Cumulative N = total number of occurrences at any time postoperative.

3. Persistent N = total number of occurrences at 12 months postoperative.

4. As the study population was comprised of glaucoma patients, this event could be related to the disease itself rather than to the IOL implant. Therefore, this ISO-defined IOL related adverse event was not analyzed here.

Table 14: Pachymetry (Available Data of Safety Population)

	Baseline	12 Months	24 Months
Cataract Surgery with iStent®			
N	111	102	104
Mean (SD)	549 (44)	555 (43)	556 (46)
Median	542	552	553
Minimum	403	419	427
Maximum	735	740	742
Missing	0	9	7
Cataract Surgery Only			
N	122	110	106
Mean (SD)	549 (37)	552 (38)	553 (37)
Median	551	549	550
Minimum	462	471	477
Maximum	627	644	636
Missing	0	12	16

N = number of eyes with non-missing values at each visit
Missing = number of eyes with data not available

Table 15: Change in Pachymetry (Consistent Cohort of Safety Population)

	Baseline to 12 Months	Baseline to 24 Months	12 Months to 24 Months
Cataract Surgery with iStent®			
N	99	99	99
Mean (SD)	7 (16)	7 (23)	0 (18)
Median	5	5	1
Minimum	-45	-74	-79
Maximum	81	112	94
Missing	12	12	12
Cataract Surgery Only			
N	104	104	104
Mean (SD)	4 (12)	4 (16)	0 (14)
Median	3	3	1
Minimum	-24	-60	-61
Maximum	39	58	46
Missing	18	18	18
2-Sample t-test for Comparing Means			
p-value	0.1456	0.2680	

N = number of eyes with non-missing values at each visit
Missing = number of eyes with data not available. Consistent cohort is the group of subjects with available data at baseline, 12 months and 24 months.

Table 16: Pachymetry by Range (Available Data for Safety Population)

	Baseline n (%)	12 Months n (%)	24 Months n (%)
Cataract Surgery with iStent®			
N	111	102	104
< 526 µm	31 (28%)	19 (19%)	21 (20%)
526 – 576 µm	57 (51%)	57 (56%)	58 (56%)
>576 µm	23 (21%)	26 (25%)	25 (24%)
Missing	0	9	7
Cataract Surgery Only			
N	122	110	106
< 526 µm	34 (28%)	26 (24%)	27 (25%)
526 – 576 µm	60 (49%)	54 (49%)	48 (45%)
>576 µm	28 (23%)	30 (27%)	31 (29%)
Missing	0	12	16

N = number of eyes with non-missing values at each visit
n = number of eyes with the corresponding responses
% = n ÷ N × 100%
Missing = Number of eyes with data not available

Table 17: Mean Pachymetry (Available Data of Non-Randomized Safety Population)

	Baseline	12 Months	24 Months
Cataract Surgery with iStent®			
N	46	44	5
Mean (SD)	547 (43)	552 (43)	567 (30)
Median	538	549	571
Minimum	433	438	518
Maximum	688	668	598
Missing/Not eligible for visit	0	2	41

N = number of eyes with non-missing values at each visit
Missing = number of eyes with data not available

Table 18: Change in Pachymetry (Consistent Cohort of Non-Randomized Population)

	Baseline to 12 Months	Baselines to 24 Months	12 Months to 24 Months
Cataract Surgery with iStent®			
N	5	5	5
Mean (SD)	6 (4)	3 (27)	-3 (24)
Median	6	3	-1
Minimum	0	-41	-41
Maximum	11	30	24
Missing	41	41	41

N = number of eyes with non-missing values at each visit
Missing = number of eyes with data not available. Consistent cohort is the group of subjects with available data at baseline, 12 months and 24 months.

Table 19: Pachymetry by Range (Available Data for Non-Randomized Population)

	Baseline n (%)	12 Months n (%)	24 Months n (%)
Cataract Surgery with iStent®			
N	46	44	5
< 526 µm	15 (33%)	12 (27%)	1 (20%)
526 – 576 µm	22 (48%)	22 (50%)	2 (40%)
>576 µm	9 (20%)	10 (23%)	2 (40%)
Missing	0	2	41

N = number of eyes with non-missing values at each visit
n = number of eyes with the corresponding responses
% = n ÷ N × 100%
Missing = Number of eyes with data not available

Table 20: Visual Field - Mean Deviation (Available Data of Safety Population)

	Baseline	6 Months	12 Months	24 Months
Cataract Surgery with iStent®				
N	114	105	104	103
Mean (SD)	-3.77 (3.03)	-3.24 (3.02)	-3.02 (2.49)	-3.22 (3.01)
Median	-3.57	-3.03	-2.98	-2.73
Minimum	-14.21	-15.33	-11.03	-12.97
Maximum	3.25	2.82	1.32	3.64
Missing	2	2	2	1
Cataract Surgery Only				
N	115	109	111	104
Mean (SD)	-3.94 (3.60)	-2.89 (3.34)	-2.81 (3.64)	-3.16 (3.66)
Median	-3.15	-1.95	-1.78	-2.39
Minimum	-16.27	-14.44	-16.83	-15.60
Maximum	2.77	2.46	2.43	2.40
Missing	2	1	1	3

Per FDA, treatment for randomized group was based on randomized assignment.
N = number of eyes with non-missing values at each visit
Missing = Number of eyes with data not available

Table 21: Change in Mean Deviation from Baseline (Available Data of Safety Population)

	6 Months n (%)	12 Months n (%)	24 Months n (%)
Cataract Surgery with iStent®			
N	104	103	102
Increase > 2.0	26 (25%)	27 (26%)	23 (23%)
No Change (-2.0 ~ 2.0)	57 (55%)	58 (56%)	63 (62%)
Decrease > 2.0	21 (20%)	18 (17%)	16 (16%)
Missing	3	3	2
Cataract Surgery Only			
N	107	109	103
Increase > 2.0	30 (28%)	36 (33%)	31 (30%)
No Change (-2.0 ~ 2.0)	62 (58%)	61 (56%)	57 (55%)
Decrease > 2.0	15 (14%)	12 (11%)	15 (15%)
Missing	3	3	4

Per FDA, treatment for randomized groups was based on randomized assignment.
N = number of eyes with non-missing values at each visit
n = number of eyes with the corresponding responses
% = n ÷ N × 100%
Missing = Number of eyes with data not available

Table 22: Visual Field - Pattern Standard Deviation (Available Data of Safety Population)

	Baseline	6 Months	12 Months	24 Months
Cataract Surgery with iStent®				
N	110	105	104	103
Mean (SD)	2.89 (1.79)	3.20 (2.07)	3.07 (2.00)	3.39 (2.29)
Median	2.23	2.34	2.35	2.46
Minimum	1.15	0.94	1.28	1.14
Maximum	11.20	10.25	11.65	11.05
Missing	6	2	2	1
Cataract Surgery Only				
N	112	109	110	104
Mean (SD)	2.79 (1.90)	3.10 (2.41)	3.06 (2.35)	3.17 (2.51)
Median	1.95	2.15	2.01	2.22
Minimum	1.10	1.13	1.24	1.05
Maximum	10.38	13.89	13.73	12.18
Missing	5	1	2	3

Per FDA, treatment for randomized group was based on randomized assignment.
N = number of eyes with non-missing values at each visit
Missing = Number of eyes with data not available

Table 23: Change in Pattern Standard Deviation from Baseline (Available Data of Safety Population)

CHANGE IN PATTERN STANDARD DEVIATION FROM BASELINE
(AVAILABLE DATA OF SAFETY POPULATION)

	6 Months n (%)	12 Months n (%)	24 Months n (%)
Cataract Surgery with iStent®			
N	105	104	103
Increase >2.0	11 (10%)	12 (12%)	18 (17%)
No Change (-2.0 - 2.0)	88 (84%)	87 (84%)	77 (75%)
Decrease >2.0	6 (6%)	5 (5%)	8 (8%)
Missing	2	2	1
Cataract Surgery Only			
N	107	108	102
Increase >2.0	14 (13%)	9 (8%)	11 (11%)
No Change (-2.0 - 2.0)	86 (80%)	93 (86%)	87 (85%)
Decrease >2.0	7 (7%)	6 (6%)	4 (4%)
Missing	3	4	5

Per FDA, treatment for randomized groups was based on randomized assignment.
N = Number of eyes with non-missing values at each visit.
n = number of eyes with the corresponding responses.
% = n ÷ N × 100%.
Missing = Number of eyes with data not available.

Table 24: Visual Field - Mean Deviation (Available Data of Non-Randomized Population)

VISUAL FIELD - MEAN DEVIATION
(AVAILABLE DATA OF NON-RANDOMIZED POPULATION)

	Baseline	6 Months	12 Months	24 Months
Cataract Surgery with iStent®				
N	45	45	44	43
Mean (SD)	-3.79 (3.92)	-2.46 (2.81)	-2.95 (2.70)	-3.38 (4.91)
Median	-2.75	-1.93	-2.45	-1.78
Minimum	-18.52	-12.53	-9.74	-26.75
Maximum	0.28	1.35	1.50	2.01
Missing	1	1	0	1

N = Number of eyes with non-missing values at each visit.
Missing = Number of eyes with data not available.

Table 25: Change in Mean Deviation from Baseline (Available Data of Non-Randomized Population)

CHANGE IN MEAN DEVIATION FROM BASELINE
(AVAILABLE DATA OF NON-RANDOMIZED POPULATION)

	6 Months n (%)	12 Months n (%)	24 Months n (%)
N	44	43	42
Increase >2.0	14 (32%)	12 (28%)	11 (26%)
No Change (-2.0 - 2.0)	24 (55%)	29 (67%)	26 (62%)
Decrease >2.0	6 (14%)	2 (5%)	5 (12%)
Missing	2	1	2

N = Number of eyes with non-missing values at each visit.
n = number of eyes with the corresponding responses.
% = n ÷ N × 100%.
Missing = Number of eyes with data not available.

Table 26: Visual Field - Pattern Standard Deviation (Available Data of Non-Randomized Population)

VISUAL FIELD - PATTERN STANDARD DEVIATION
(AVAILABLE DATA OF NON-RANDOMIZED POPULATION)

	Baseline	6 Months	12 Months	24 Months
Cataract Surgery with iStent®				
N	46	45	44	42
Mean (SD)	2.48 (1.61)	2.41 (1.49)	2.55 (1.41)	2.98 (2.05)
Median	1.90	2.21	2.13	2.24
Minimum	1.13	1.11	1.00	1.14
Maximum	10.23	9.86	7.23	9.58
Missing	0	1	0	2

N = Number of eyes with non-missing values at each visit.
Missing = Number of eyes with data not available.

Table 27: Change in Pattern Standard Deviation from Baseline (Available Data of Non-Randomized Population)

CHANGE IN PATTERN STANDARD DEVIATION FROM BASELINE
(AVAILABLE DATA OF NON-RANDOMIZED POPULATION)

	6 Months n (%)	12 Months n (%)	24 Months n (%)
N	45	44	42
Increase >2.0	1 (2%)	1 (2%)	6 (14%)
No Change (-2.0 - 2.0)	41 (91%)	41 (93%)	34 (81%)
Decrease >2.0	3 (7%)	2 (5%)	2 (5%)
Missing	1	0	2

N = Number of eyes with non-missing values at each visit.
n = number of eyes with the corresponding responses.
% = n ÷ N × 100%.
Missing = Number of eyes with data not available.

Table 28: Test of the Primary Effectiveness Endpoints at 12 months postoperatively (analyses based upon randomization) (conducted by FDA)

	Treatment Group (n=116)	Control Group (n=123)	p-value[1]
Non-Responder (ITT)	79/116 (68.10%)	61/123 (49.59%)	**0.0040**
Complete-Case	79/108 (73.15%)	61/112 (54.46%)	**0.0050**
Worst-Case (ITT)	79/116 (68.10%)	72/123 (58.54%)	**0.1410**

1. P-values in this table are from 2-sided Fisher's exact test

Table 29: Tipping-point Analysis for the Primary Effectiveness Endpoint at 12 Months Postoperatively (analyses based upon randomization) (conducted by FDA)

		Control Group (# of assumed successes among 11 missing subjects)											
		0	1	2	3	4	5	6	7	8	9	10	11
Treatment Group (# of assumed successes among 8 missing subjects)	0	**NON-RESPONDER**											**WORST CASE**
	1												
	2												
	3												
	4									**"WORST REASONABLE"**			
	5												
	6							**"BEST REASONABLE"**					
	7												
	8	**BEST CASE**											

Table 30: Test of the Primary Effectiveness Endpoints at 12 months postoperative (As-Treated) (conducted by FDA)

	Treatment Group (n=111)	Control Group (n=121)	p-value
Non-Responder	79/111 (71.17%)	61/121 (50.41%)	**0.0013**
Complete-Case	79/106 (74.53%)	61/114 (53.51%)	**0.0013**
Worst-Case	79/111 (71.17%)	66/121 (54.55%)	**0.0101**

1. Using 2-sided Fisher exact test

Table 31: Tipping-point Analysis for the Primary Effectiveness Endpoint at 12 Months Postoperatively (As-Treated) (conducted by FDA)

		Control Group (# of assumed successes among 7 missing subjects)							
Treatment Group (# of assumed successes among 5 missing subjects)		0	1	2	3	4	5	6	7
	0	**NON-RESPONDER**							**WORST CASE**
	1								
	2								
	3						**"WORST REASONABLE"**		
	4					**"BEST REASONABLE"**			
	5	**BEST CASE**							

Table 32: Test of the Primary Effectiveness Endpoints at 24 months postoperatively (analyses based upon randomization) (conducted by FDA)

	Treatment Group (n=116)	Control Group (n=123)	p-value
Non-Responder (ITT)	65/116	57/123	**0.1549**
Complete-Case	65/106	57/107	**0.2686**
Worst-Case (ITT)	65/116	73/123	**0.6944**

Table 33: Test of the Primary Effectiveness Endpoints at 24 months postoperatively (As-Treated) (conducted by FDA)

	Treatment Group (n=111)	Control Group (n=121)	p-value
Non-Responder	65/111	57/121	**0.0884**
Complete-Case	65/104	57/109	**0.1658**
Worst-Case	65/111	67/121	**0.6909**

Table 34: Test of the Secondary Effectiveness Endpoints at 12 months postoperatively Using 20% (analyses based upon randomization) (conducted by FDA)

	Treatment Group (n=116)	Control Group (n=123)	p-value
Non-Responder (ITT)	74/116 (63.79%)	58/123 (47.15%)	**0.0133**
Complete-Case	74/108 (68.52%)	58/112 (51.79%)	**0.0133**
Worst-Case (ITT)	74/116 (63.79%)	69/123 (56.10%)	**0.2375**

Table 35: Tipping-point Analysis for the Secondary Effectiveness Endpoint at 12 months postoperative Using 20% (analyses based upon randomization) (conducted by FDA)

		Control Group (missing n=11)											
		0	1	2	3	4	5	6	7	8	9	10	11
Treatment Group (missing n=8)	0	**NON-RESPONDER**											**WORST CASE**
	1												
	2												
	3												
	4									**"WORST REASONABLE"**			
	5												
	6							**"BEST REASONABLE"**					
	7												
	8	**BEST CASE**											

Table 36: Test of the Secondary Effectiveness Endpoints at 12 months postoperatively Using 20% (As-Treated) (conducted by FDA)

	Treatment Group (n=111)	Control Group (n=121)	p-value
Non-Responder	74/111 (66.67%)	58/121 (47.93%)	**0.0052**
Complete-Case	74/106 (69.81%)	58/114 (50.88%)	**0.0058**
Worst-Case	74/111 (66.67%)	63/121 (52.07%)	**0.0323**

Table 37: Test of the Secondary Effectiveness Endpoints at 24 months postoperative Using 20% (analyses based upon randomization) (conducted by FDA)

	Treatment Group (n=116)	Control Group (n=123)	p-value
Non-Responder (ITT)	57/116 (49.14%)	49/123 (39.84%)	**0.1545**
Complete Case	57/106 (53.77%)	49/107 (44.95%)	**0.2740**
Worst-Case (ITT)	57/116 (49.14%)	65/123 (52.85%)	**0.6057**

Table 38: Percent of Subjects Achieving IOP Reduction Outcomes at 12 Months ("analyses based upon randomization" with Non-Responder Approach)

PERCENT OF SUBJECTS ACHIEVING IOP REDUCTION OUTCOMES AT 12 MONTHS
ITT WITH NON-RESPONDER APPROACH

	Randomized		Non-Randomized	Difference and 90% CI of Difference		
	Cataract Surgery with iStent® [1] n/N (%) (90% CI)	Cataract Surgery Only [2] n/N (%) (90% CI)	Cataract Surgery with iStent® [3] n/N (%) (90% CI)	[1] vs. [2]	[1] vs. [3]	[3] vs. [2]
IOP ≤21 mmHg Without medication	79/116 (68%) (61%,75%)	61/123 (50%) (42%,57%)	36/46 (78%) (68%,88%)	19% (8%, 29%)	-10% (-22%, 2%)	29% (16%, 41%)
IOP reduction ≥20% Without medication	74/116 (64%) (56%,71%)	58/123 (47%) (40%,55%)	33/46 (72%) (61%,83%)	17% (6%, 27%)	-8% (-21%, 5%)	25% (11%, 38%)
IOP reduction ≥30% Without medication	47/116 (41%) (33%,48%)	34/123 (28%) (21%,34%)	23/46 (50%) (38%,62%)	13% (3%, 23%)	-9% (-24%, 5%)	22% (9%, 36%)
IOP ≥6 mmHg Without medication, < 10 letters BCVA loss, No AE through 12 months, and IOP reduction ≥20%	43/116 (37%) (30%,44%)	32/123 (26%) (20%,33%)	16/46 (35%) (23%,46%)	11% (1%, 21%)	2% (-11%, 16%)	9% (-4%, 22%)
IOP ≥6 mmHg without medication, < 10 letters BCVA loss, No AE through 12 months, and IOP Reduction achieving corresponding target[1]	45/116 (39%) (31%,46%)	34/123 (28%) (21%,34%)	16/46 (35%) (23%,46%)	11% (1%, 21%)	4% (-10%, 18%)	7% (-6%, 20%)
IOP ≥6 mmHg Without medication, < 10 letters BCVA loss, No AE through 12 months, and IOP decreased from baseline ≥3 mmHg	49/116 (42%) (35%,50%)	34/123 (28%) (21%,34%)	17/46 (37%) (25%,49%)	15% (5%, 25%)	5% (-9%, 19%)	9% (-4%, 23%)
IOP ≥6 mmHg Without medication, < 10 letters BCVA loss, No severe AE through 12 months, and IOP reduction ≥20%	72/116 (62%) (55%,69%)	58/123 (47%) (40%,55%)	32/46 (70%) (58%,81%)	15% (4%, 25%)	-7% (-21%, 6%)	22% (9%, 36%)
IOP ≥6 mmHg without medication, < 10 letters BCVA loss, No severe AE through 12 months, and IOP Reduction achieving corresponding target[1]	74/116 (64%) (56%,71%)	60/123 (49%) (41%,56%)	33/46 (72%) (61%,83%)	15% (5%, 25%)	-8% (-21%, 5%)	23% (10%, 36%)
IOP ≥6 mmHg Without medication, < 10 letters BCVA loss, No severe AE through 12 months, and IOP decreased from baseline ≥3 mmHg	78/116 (67%) (60%,74%)	62/123 (50%) (43%,58%)	35/46 (76%) (66%,86%)	17% (7%, 27%)	-9% (-21%, 4%)	26% (13%, 38%)

With Special Cases Handled per Suggestions from FDA. Subjects who underwent secondary procedures are considered to be non-responders. Secondary procedures include stent reposition, stent explant/replacement, 2 stents implanted, deep sclerectomy, trabeculoplasty, LASIK, and iridoplasty for stent obstruction. [redacted] (randomized to iStent) was excluded from the analysis per FDA's suggestion. The fellow eye of the subject was treated and included in the analysis.

For subjects without the measurement, non-responder outcome was assumed.

1 At least 15% reduction in IOP from baseline, if the baseline IOP ≤24 mmHg. At least 20% reduction in IOP from baseline, if the baseline IOP is 25 - 29 mmHg. At least 30% reduction in IOP from baseline, if the baseline IOP ≥30 mmHg.

Database frozen date: 05/17/2010

Table 39: Percent of Subjects Achieving IOP Reduction Outcomes at 12 Months Stratified by Glaucoma Type

(analyses based upon randomization with non-responder approach)

	Pigmentary or Pseudoexfoliative Glaucoma		Other Open Angle Glaucoma	
	Randomized Cataract Surgery with iStent®	Randomized Cataract Surgery Only	Randomized Cataract Surgery with iStent®	Randomized Cataract Surgery Only
	n/N (%) (90% CI)	n/N (%) (90% CI)	n/N (%) (90% CI)	n/N (%) (90% CI)
IOP ≤21 mmHg Without medication	5/11 (45%) (21%, 70%)	3/10 (30%) (6%, 54%)	74/105 (70%) (63%, 78%)	58/113 (51%) (44%, 59%)
IOP reduction ≥20% Without medication	6/11 (55%) (30%, 79%)	2/10 (20%) (0%, 41%)	68/105 (65%) (57%, 72%)	56/113 (50%) (42%, 57%)
IOP reduction ≥30% Without medication	5/11 (45%) (21%, 70%)	1/10 (10%) (0%, 26%)	42/105 (40%) (32%, 48%)	33/113 (29%) (22%, 36%)
IOP ≥6 mmHg Without medication, < 10 letters BCVA loss, No AE through 12 months, and IOP reduction ≥20%	2/11 (18%) (0%, 37%)	1/10 (10%) (0%, 26%)	41/105 (39%) (31%, 47%)	31/113 (27%) (21%, 34%)
IOP ≥6 mmHg without medication, < 10 letters BCVA loss, No AE through 12 months, and IOP Reduction achieving corresponding target[1]	2/11 (18%) (0%, 37%)	1/10 (10%) (0%, 26%)	43/105 (41%) (33%, 49%)	33/113 (29%) (22%, 36%)
IOP ≥6 mmHg Without medication, < 10 letters BCVA loss, No AE through 12 months, and IOP decreased from baseline ≥3 mmHg	2/11 (18%) (0%, 37%)	1/10 (10%) (0%, 26%)	47/105 (45%) (37%, 53%)	33/113 (29%) (22%, 36%)
IOP ≥6 mmHg Without medication, < 10 letters BCVA loss, No severe AE through 12 months, and IOP reduction ≥20%	5/11 (45%) (21%, 70%)	2/10 (20%) (0%, 41%)	67/105 (64%) (56%, 72%)	56/113 (50%) (42%, 57%)
IOP ≥6 mmHg without medication, < 10 letters BCVA loss, No severe AE through 12 months, and IOP Reduction achieving corresponding target[1]	5/11 (45%) (21%, 70%)	1/10 (10%) (0%, 26%)	69/105 (66%) (58%, 73%)	59/113 (52%) (44%, 60%)
IOP ≥6 mmHg Without medication, < 10 letters BCVA loss, No severe AE through 12 months, and IOP decreased from baseline ≥3 mmHg	5/11 (45%) (21%, 70%)	2/10 (20%) (0%, 41%)	73/105 (70%) (62%, 77%)	60/113 (53%) (45%, 61%)

With Special Cases Handled per Suggestions from FDA. Subjects who underwent secondary procedures are considered to be non-responders. Secondary procedures include stent reposition, stent explant/replacement, 2 stents implanted, deep sclerectomy, trabeculoplasty, LASIK, and iridoplasty for stent obstruction. [redacted] (randomized to iStent) was excluded from the analysis per FDA's suggestion. The fellow eye of the subject was treated and included in the analysis.

For subjects without the measurement, non-responder outcome was assumed.

1 At least 15% reduction in IOP from baseline, if the baseline IOP ≤24 mmHg. At least 20% reduction in IOP from baseline, if the baseline IOP is 25 - 29 mmHg. At least 30% reduction in IOP from baseline, if the baseline IOP ≥30 mmHg.

Table 40: Patient Enrollment by Participating Site

Site ID	Enrollment	Percentage	Ranking
1	3	1.25%	18
3	27	11.15%	2
9	2	0.83%	20
11	4	1.67%	14
16	11	4.58%	8
17	2	0.83%	20
18	20	8.33%	4
19	18	7.50%	5
22	14	5.83%	7
23	11	4.58%	8
24	4	1.67%	14
25	10	4.17%	10
26	1	0.42%	24
28	1	0.42%	24
29	2	0.83%	20
32	9	3.75%	11
34	1	0.42%	24
38	24	10.00%	3
39	1	0.42%	24
41	3	1.25%	18
42	9	3.75%	11
43	15	6.25%	6
45	4	1.67%	14
46	5	2.08%	13
47	33	13.75%	1
48	4	1.67%	14
49	2	0.83%	20
Total	240	100%	

Table 41: IOP ≤ 21 mmHg without Anti-Glaucoma Medications at 12 Months by Site (Excluding Observed Outcomes after Secondary Procedures) (ITT Population with LOCF for Missing Data)

Site	Cataract Surgery with iStent® n/N (%) (90% CI)	Cataract Surgery Only n/N (%) (90% CI)	P-Value[1]
03 **(n=27)**	9/13 (69%) (48%, 90%)	8/14 (57%) (35%, 79%)	0.984
16 **(n=11)**	5/6 (83%) (58%, 100%)	1/5 (20%) (0%, 49%)	
18 **(n=20)**	9/10 (90%) (74%, 100%)	4/10 (40%) (15%, 65%)	
19 **(n=18)**	8/9 (89%) (72%, 100%)	4/9 (44%) (17%, 72%)	
22 **(n=14)**	3/6 (50%) (16%, 84%)	2/8 (25%) (0%, 50%)	
23 **(n=11)**	4/5 (80%) (51%, 100%)	4/6 (67%) (35%, 98%)	
25 **(n=10)**	4/5 (80%) (51%, 100%)	2/5 (40%) (4%, 76%)	
38 **(n=24)**	10/12 (83%) (66%, 100%)	4/12 (33%) (11%, 56%)	
43 **(n=15)**	3/7 (43%) (12%, 74%)	3/8 (38%) (9%, 66%)	
47 **(n=33)**	12/16 (75%) (57%, 93%)	14/17 (82%) (67%, 98%)	
01, 09, 11, 17, 24, 26, 28, 29, 32, 34, 39, 41, 42, 45, 46, 48, 49	18/28 (64%) (49%, 79%)	15/29 (52%) (36%, 67%)	

Secondary procedures include stent reposition, stent explant/replacement, 2 stents implanted, deep sclerectomy, replaced IOL, trabeculoplasty, pars plana vitrectomy, and iridoplasty for stent obstruction.
Observed IOP after secondary procedures was treated as missing. Subjects with anti-glaucoma medications were treated as a non-responder regardless of receiving with secondary surgical intervention.
Sites with a size of < 10 were pooled.
1 Two-sided Gail-Simon test.

Table 42: Interaction between Treatment and Site Size (Four Largest Sites vs. Other Small Sites) (conducted by FDA)

p-values	Treatment (p-value)	Site Size (p-value)	Interaction between Treatment and Site Size (p-value)
Primary Effectiveness Endpoint	0.0152	0.8392	0.7228
Secondary Effectiveness Endpoint Using 20%	0.0299	0.8762	0.6972
Secondary Effectiveness Endpoint Using 30%	0.3284	0.6772	0.3970

Appendix 1: Special Cases

Subjects randomized to iStent arm:

- ***Subject [redacted] and Subject [redacted]***: These two "subjects" are actually the two eyes of the same subject. "Subject [redacted]" is the initial eye enrolled into the study. This eye was randomized to the iStent. However, the stent was not implanted due to complications during the cataract surgery. The protocol states in Section 9.6.3 Surgical Procedure, "Successful and uncomplicated cataract surgery is required for each subject enrolled in this study. If there are complications during the cataract extraction or IOL implantation procedure that would be significant enough to impact the study results, the subject should be exited from the study. One of the exclusion criteria outlined in the protocol is "Fellow eye actively enrolled". It appears that this eye was exited from the study after cataract surgery and that the second eye was enrolled ("Subject [redacted]). The second eye was also randomized to cataract surgery with the iStent. Clinically, it is believed that the two eyes from one patient are highly correlated so that the clinical outcomes are very likely similar. Therefore, the first eye ("Subject [redacted]) should not be considered as missing or a failure for the effectiveness analyses, but rather data from the second eye ("Subject [redacted]") should be included in the effectiveness analyses and considered a replacement. Both eyes should be included in the safety analyses.
- ***Subject [redacted]***: Subject had stent repositioning for stent obstruction (partial occlusion by iris). This case should be considered a failure for the primary and secondary effectiveness analyses, not missing. (This subject is one of those in the randomized cohort that has pseudoexfoliative glaucoma).
- ***Subjects [redacted], [redacted], and [redacted]***: These subjects had complicated cataract surgery and were discontinued from the study. These subjects should be treated as missing for the effectiveness analyses and should be included in the iStent group for the safety analyses for their intraoperative complications. [It should be noted that one other subject had complicated cataract surgery but was implanted with the stent and completed the 12- and 24-month visits rather than being discontinued.]
- ***Subject [redacted]***:Subject had stent repositioning for migration of the stent out of Schlemm's canal. This case should be considered a failure for the primary and secondary effectiveness analyses, not missing. (This subject had pigmentary glaucoma.)
- ***Subject [redacted]***: Subject had stent repositioning for migration of the stent out of Schlemm's canal. This case should be considered a failure for the primary and secondary effectiveness analyses, not missing. Fifteen months after the initial surgery, this subject underwent trabeculoplasty. Selective laser trabeculoplasty (SLT) was also performed after the 24-month visit.
- ***Subject [redacted]***: The first stent implanted in this subject was malpositioned. The IOP increased and IOP-lowering medications were added. The first stent was removed and a second stent was implanted. This subject should be considered a failure for the primary and secondary effectiveness analyses (and not missing), since the initial implantation was a failure.
- ***Subject [redacted]***: This subject was discontinued from the study prior to surgery. This subject should be considered missing for both the effectiveness and safety analyses.

- ***Subject*** [redacted]: The investigator was unable to implant the stent. The subject was discontinued from the study. This case should be considered a failure for the effectiveness analyses, since there was failure to be able to implant the stent. This subject should be included in the iStent group for the safety analyses, since inability to implant the stent can be considered a complication of the surgery.
- ***Subject*** [redacted]: This subject had two stents implanted, because the first was malpositioned. This case should be considered a failure for the primary and secondary effectiveness analyses, not missing, since the first stent was malpositioned.
- ***Subject*** [redacted]: Subject had laser iridoplasty for stent obstruction by the iris. This case should be considered a failure for the primary and secondary effectiveness analyses, not missing.

Subjects randomized to the control arm:

- ***Subjects*** [redacted], [redacted], ***and*** [redacted]: These subjects had complicated cataract surgery and were discontinued from the study. These subjects should be treated as missing for the effectiveness analyses and should be included in the cataract surgery only group for the safety analyses for their intraoperative complications. [It should be noted that one other subject had complicated cataract surgery but completed the 12- and 24-month visits rather than being discontinued.]
- ***Subject*** [redacted]: Subject had deep sclerectomy. This case should be considered a failure for the primary and secondary effectiveness analyses, not missing . (After deep sclerectomy, the subject also underwent laser sclerostomy and then developed choroidal detachment which spontaneously resolved.)
- ***Subject*** [redacted]: This subject had an intraoperative complication. The trailing haptic got torn, and the investigator enlarged the incision to remove and replace the IOL. There was a positive Seidel noted 3 hours postoperatively and the subject was returned to the OR to resuture the wound. At 3 months, the subject underwent pupilloplasty for visual symptoms secondary to an enlarged pupil. Sixteen months after the initial surgery, the subject underwent IOL removal and replacement for “poor near vision”. This case should not be considered a failure or missing for the effectiveness analyses based upon one of these secondary surgical interventions.
- ***Subject*** [redacted]: This subject had LASIK 9 months after the initial surgery for an unanticipated hyperopic cataract surgery outcome. The subject did not fail the primary or secondary effectiveness endpoints at 1 year postoperatively. However, FDA believes that the IOP measurement may be artificially low due to the LASIK treatment. Therefore, this subject should be treated as missing for the primary and secondary effectiveness analyses at 1 year. The subject was on one medication at the 24-month visit and should be treated as a failure for purposes of the effectiveness analyses at this time point.
- ***Subject*** [redacted]: This subject was treated with trabeculoplasty twice, the first time at the 3-month visit. This case should be considered a failure for the primary and secondary effectiveness analyses, not missing due to trabeculoplasty.
- ***Subject*** [redacted]: This subject underwent pars plana vitrectomy with membrane peel and endolaser for treatment of a stage VI macular hole. This case should not be considered a

failure or missing for the effectiveness analyses based upon the secondary surgical intervention.

- ***Subject*** [redacted]: This case should be considered a failure for the primary and secondary effectiveness analyses, not missing due to SLT.

Additional Special Cases with respect to effectiveness analyses at 2 years:

- ***Subject*** [redacted]: At an interim visit (427 days after the initial surgery), stent obstruction was reported in this subject. The subject underwent Nd:YAG laser treatment for stent obstruction to remove a "membrane-like material" from the stent ostium. Travatan was prescribed, because the pressure was still high despite clearing of the ostium.

- ***Subject*** [redacted]: This subject was randomized to the control arm and had SLT 3 weeks after the 24-month visit due to IOP of 25 mmHg on 3 medications at the 24-month visit.

Table 43: Subjects With Final BCVA ≥ 2 lines Worse Than Best BCVA AND Worse Than 20/32

Group*	Subject #	Best BCVA	Final BCVA	AE Case Summary	Additional Detail
1	[redacted]	20/17	20/35	na	Preop ARMD. No AEs reported. Final BCVA = 20/35
1	[redacted]	20/17	20/38	na	Preop choroidal nevus; no AEs reported. Final BCVA = 20/38
1	[redacted]	20/32	count fingers	yes	AEs: BCVA loss due to carotid stenosis and cerebrovascular event; stroke
1	[redacted]	20/23	20/33	no	Preop ocular allergies + floaters; AE: dysesthesia/photophobia. Final BCVA = 20/33
1	[redacted]	20/25	20/66	na	No apparent pathology, no AEs. Fellow eye BCVA (screening) =20/50. Final BCVA = 20/66
1	[redacted]	20/17	20/46	yes	Preop dry eye. VF decrease. Final BCVA = 20/46
1	[redacted]	20/17	20/33	na	Preop dry eye. No AEs. Final BCVA = 20/33
1	[redacted]	20/22	20/36	na	Preop allergic conjunctivitis + drusen. No AE. Final BCVA = 20/36
2	[redacted]	20/29	20/100	yes	Preop ARMD; worsened over time. Per retinal specialist @M18, BCVA loss was due to severe RPE disease and drusen.
2	[redacted]	20/25	20/42	no	Preop ARMD + SPK. Final BCVA = 20/42
2	[redacted]	20/14	20/46	no	M24 BCVA = 20/46. At M24, pco noted and Nd:YAG laser performed
2	[redacted]	20/17	20/50	yes	No apparent pathology. No relevant AEs. Final BCVA = 20/50
2	[redacted]	20/20	20/35	na	No apparent pathology. No AEs. Final BCVA = 20/35
2	[redacted]	20/20	20/33	no	Preop drusen. No relevant AEs. Final BCVA = 20/33
2	[redacted]	20/26	20/46	no	Preop dry eye. AE: blurry vision. Final BCVA = 20/46
2	[redacted]	20/19	20/35	yes	AEs: iritis and blurry vision. Final BCVA = 20/35

2	[redacted]	20/21	20/36	yes	AE: BCVA loss (blurred vision, dizziness+floaters) after closed head trauma. Final BCVA = 20/36
2	[redacted]	20/20	20/33	no	Preop dry eye; development of proliferative diabetic retinopathy. Final BCVA = 20/33
3	[redacted]	20/20	20/33	no	No apparent pathology. No relevant AEs. Final BCVA = 20/33
3	[redacted]	20/22	20/46	no	Epiretinal membrane (2009); pco treated with YAG (2008)
3	[redacted]	20/21	20/63	no	No apparent pathology. AE: vitreous floaters. Final BCVA = 20/63

*Group 1 = randomized to cataract surgery + iStent; Group 2 = randomized to cataract surgery only; Group 3 = non-randomized cataract surgery + iStent

Appendix 2: OUS studies done with prior models

- **GC-001A** was a prospective, open-label, non-randomized European study of refractory glaucoma subjects. 43 subjects were ultimately implanted. There were multiple adverse events, and 22 secondary surgical interventions in 19 subjects. Subjects with prior glaucoma procedures were enrolled, however not all subjects enrolled meet FDA definitions of "refractory". Lack of a control arm and confounding use of medications made effectiveness outcomes difficult to interpret.
- US IDE ---------- (**GC-001B**) was a prospective, open-label, non-randomized study of refractory glaucoma subjects. Nine subjects were enrolled. There was an unacceptably wide range of clinical response to the device and an uncertain expectation of effectiveness. Enrollment was terminated early due to, significant IOP elevation in eyes at risk for serious optic nerve damage and visual field losses.. The final report of this clinical study was submitted November 2008. Two of the nine subjects were discontinued due to trabeculectomy and device removal. Three trabeculectomies total and 2 glaucoma shunt procedures were performed as secondary surgical procedures. Changes in intraocular pressure ranged from a 36% reduction to a 19% increase in intraocular pressure in the US and range of 53% reduction to 56% increase IOP in EU study. There was a 44% incidence of IOP reduction at least 20%).
- **GC-002** was a prospective, non-randomized, open-label study of EU subjects with OAG. Subjects had to be on at least one glaucoma medication and had to have IOP > 18 mmHg. 57/59 enrolled subjects were ultimately implanted with the device. Subjects undergoing secondary surgical interventions and subjects not meeting enrollment criteria (n=5) were excluded from effectiveness analyses. 41/57 subjects were included in analysis. Of the 41 subjects considered evaluable at 24 months, 21 had IOP < 18 mmHg on no medications, and the same number met these criteria at 12 months. Of the 41 "qualified" subjects, there were 40 with the same or fewer medications compared to baseline at 24 months postoperatively. Thirty-three of these subjects had a decrease in IOP from baseline at this time point and 4 had no change in IOP from baseline. Three of these subjects had an increase in IOP from baseline.
- **GCF-004** was a single-site study conducted in Australia in five subjects with OAG. 2/3 implanted with the previous device design were implanted with 2 stents without cataract surgery; 1/3 was implanted with 1 stent in conjunction with cataract surgery. One subject received a stent design never used in the USA in conjunction with cataract surgery; and one additional subject underwent cataract surgery alone. Follow up ranged from 1 to 5.5 months. At the last visit for the 3 eyes implanted with the prior stent design, 1 subject had no change in the IOP from baseline of 22 mmHg and an increase in medications by 1; 1 subject had a decrease in IOP from 32 to 15.5 mmHg with no change in the number of medications; and 1 had an increase in IOP from 23 to 24 mmHg with an increase in the number of medications by 1.

Appendix 3: OUS studies involving the current stent and inserter design

GCF-005:

- Prospective, open-label, multicenter investigation conducted in the EU and Turkey
- 62 patients with open-angle glaucoma (OAG) on at least one medication.
- Randomized into 2 groups:
  - Group 1: to be implanted with 1 stent,
  - Group 2: to be implanted with 2 stents.
- 32 subjects were enrolled in Group 1; 3 subjects in this group received a second stent to achieve the target IOP of at least 18 mmHg.
- 31 subjects were randomized to Group 2. One subject in this group did not receive a stent due to patient anatomy.
- A diurnal sub-study was performed on 23 subjects, but only 7 subjects in each group were considered evaluable.

Results:

- 23 (71.9%) Group 1 subjects and 17 (56.7%) Group 2 subjects completed the 12-month visit
- 18 Group 1 and 12 Group 2 subjects completed the 24-month visit with subjects still active at this visit.
- 2 Group 2 subjects were discontinued: one underwent trabeculectomy for elevated IOP; another experienced stent obstruction that could not be cleared by Argon laser.

Adverse events:

Group 1: 21 adverse events reported during the 24-month follow-up period.

- Iris damage occurred during implantation one subject.
- 8 reports of stent obstruction in 6 eyes.
- Secondary surgical intervention in 3 eyes (2 trabeculectomies, 1 undefined) due to elevated IOP.
- Other: stent malposition without intervention; stent malposition with explantation and replacement with a new stent; and mobilization of the iris with viscoelastic.

Group 2: 22 adverse events were reported during the 24-month follow-up period.

- 4 intraoperative events: inability to implant a stent due to anatomy; iris prolapse through the paracentesis; significant hyphema, and implantation of a left stent in a right eye.
- 3 reports of stent obstruction
- 5 eyes required secondary surgical intervention (trabeculectomy) due to elevated IOP.
- Other: significant postop hyphema and inflammation in one eye each.

Subjects requiring secondary surgical intervention or stent enhancement were included in the effectiveness analysis up until the last follow-up exam prior to the secondary intervention. Success was defined as either a reduction in IOP or a reduction in medication from baseline. Thirteen Group 1 subjects and 14 Group 2 subjects were considered a success at 12 months. Follow-up is on-going.

GCF-006:

- Open-label, single-site study: 11 subjects in Turkey with OAG and IOP > 22 mmHg
- Randomized to:
  - Group 1: implantation with 2 stents (8 subjects/16 stents)

- Group 2: anti-glaucoma medications only (3 subjects).
- 7 Group 1 and 2 Group 2 subjects were available for analysis at 12 months
- 6 Group 1 and 2 Group 2 subjects were available for analysis at 24 months.
- 6/7 Group 1 subjects and 2/2 Group 2 subjects had IOP reductions from baseline at 12 months;
  - Reductions were achieved in the Group 1 subjects with stent implantation alone without any IOP-lowering medications.
  - Mean IOP for Group 1 subjects was 23.6 (SD 1.5) at baseline, 20.1 (SD 2.8) at 12 months and 17.3 (SD 2.7) at 24 months.

There were no adverse events reported in the Group 1 subjects at any time up to this report.

GCF-007:

- Prospective, concurrently controlled, open-label, multi-center study in the EU and Turkey
- 50 subjects undergoing cataract surgery with newly diagnosed OAG, ocular hypertension, or mild glaucoma.
- Randomized:
  - Group 1: 2 stents implanted following cataract surgery (27/50 subjects)
  - Group 2: glaucoma medications after cataract surgery only (23/50subjects)
- Follow-up period: 5 years for EU subjects and 24 months for Turkish subjects.
- EU subjects had washout of glaucoma medications prior to surgery: Turkish subjects did not.
- Enrollment criteria differed between the 2 groups.
- Despite these differences, the applicant has pooled the data from the 39 EU subjects (35 from 1 site) and 11 Turkish subjects.

- 19 (70.4%) Group 1 subjects and 14 (60.9%) Group 2 subjects completed the 12-month visit.
- 12 (44.4%) Group 1 subjects and 13 (56.5%) Group 2 subjects completed the 24-month visit. Subjects were still active at the 24-month visit.

Secondary Interventions:

- Intraoperative: vitrectomy secondary to posterior bag rupture in one group 2 subject.
- Trabeculectomy: 1 Group 1 subject and 1 Group 2 subject. This Group 1 subject had "intractable IOP due to PAS" and was discontinued from the study.
- Trabeculoplasty: 2 Group 2 subjects.
- Malpositioned stents: 3 group 1 subjects

Subjects requiring secondary surgical intervention were included in the effectiveness analysis up until the last follow-up exam prior to the intervention.

- All 18 evaluable Group 1 subjects showed a reduction of IOP at 12 months with reduced medication use.
- All 11 evaluable Group 2 subjects showed a reduction of IOP at 12 months; 8 of the 11 had reduced medication use.
- At 24 months, all of the 11 evaluable Group 1 subjects had reduced IOP, and 8/11 had reduced medication use.
- All 12 evaluable Group 2 subjects at 24 months showed reduced IOP with 8/12 showing reduced medication use.
- The applicant did not state by how much the IOP had been reduced.

- Subjects were still active at the time of this report.

In addition to the OUS studies, a total of 34 eyes have been implanted with the GTS100R/L stent by Dr. Ike Ahmed in Canada under the Special Access Program. These devices were not implanted under a clinical study protocol, and data are not being collected by Glaukos. According to the applicant, adverse event reporting under the Canadian Medical Device Regulations is required, and to their knowledge, Dr. Ahmed has not reported any adverse events as of the time of the original PMA submission.

Also, case report forms for a total of 16 subjects were submitted to the European database Netregulus as part of a postmarket study for the CE marked GTS100 stent system. A total of 9 subjects submitted 1-year case report forms. No adverse events were reported for any of the subjects.