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Prospective, Randomized, Controlled Pivotal Trial of an *Ab Interno* Implanted Trabecular Micro-Bypass in Primary Open-Angle Glaucoma and Cataract

Two-Year Results

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Purpose: Evaluate the safety and effectiveness of an *ab interno* implanted (iStent *inject*) Trabecular Micro-Bypass System (Glaukos Corporation, San Clemente, CA) in combination with cataract surgery in subjects with mild to moderate primary open-angle glaucoma (POAG).

Design: Prospective, randomized, single-masked, concurrently controlled, multicenter clinical trial.

Participants: Eyes with mild to moderate POAG and preoperative intraocular pressure (IOP) ≤24 mmHg on 1 to 3 medications, unmedicated diurnal IOP (DIOP) 21 to 36 mmHg, and cataract requiring surgery.

Methods: After uncomplicated cataract surgery, eyes were randomized 3:1 intraoperatively to *ab interno* implantation of iStent *inject* (Model G2-M-IS; treatment group, n = 387) or no stent implantation (control group, n = 118). Subjects were followed through 2 years postoperatively. Annual washout of ocular hypotensive medication was performed.

Main Outcome Measures: Effectiveness end points were ≥20% reduction from baseline in month 24 unmedicated DIOP and change in unmedicated month 24 DIOP from baseline. Safety measures included best spectacle-corrected visual acuity (BSCVA), slit-lamp and fundus examinations, gonioscopy, pachymetry, specular microscopy, visual fields, complications, and adverse events.

Results: The groups were well balanced preoperatively, including medicated IOP (17.5 mmHg in both groups) and unmedicated DIOP (24.8±3.3 mmHg vs. 24.5±3.1 mmHg in the treatment and control groups, respectively, $P = 0.33$). At 24 months, 75.8% of treatment eyes versus 61.9% of control eyes experienced ≥20% reduction from baseline in unmedicated DIOP ($P = 0.005$), and mean reduction in unmedicated DIOP from baseline was greater in treatment eyes (7.0±4.0 mmHg) than in control eyes (5.4±3.7 mmHg; $P < 0.001$). Of the responders, 84% of treatment eyes and 67% of control eyes were not receiving ocular hypotensive medication at 23 months. Furthermore, 63.2% of treatment eyes versus 50.0% of control eyes had month 24 medication-free DIOP ≤18 mmHg (difference 13.2%; 95% confidence interval, 2.9−23.4). The overall safety profile of the treatment group was favorable and similar to that in the control group throughout the 2-year follow-up.

Conclusions: Clinically and statistically greater reductions in IOP without medication were achieved after iStent *inject* implantation with cataract surgery versus cataract surgery alone, with excellent safety through 2 years. *Ophthalmology 2019;126:811-821 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Glaucoma is the leading cause of irreversible blindness worldwide, currently affecting more than 44.7 million people and increasing to 58.6 million by 2020.[1,2] Most therapies target intraocular pressure (IOP) reduction, the only clinically proven method to slow progression of optic nerve damage. Even modest IOP reductions have benefit, as shown by an 11% to 19% decreased disease progression risk for each 1 mmHg IOP reduction.[3,4]

Recently, micro-invasive glaucoma surgery (MIGS) procedures have been shown to provide sustained IOP reduction without the disadvantages of ocular hypotensive medication (e.g., poor compliance, ocular surface disease,

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cost) or the substantial additional risk associated with filtering surgeries, such as decreased visual acuity, bleb infections, and lifetime risk of endophthalmitis.[5] Trabecular micro-bypass devices implanted *ab internally* are designed to optimize the natural physiologic outflow of aqueous humor. Note, trabecular stent implantation does not preclude additional medical or surgical therapies that may become necessary in the future.

Clinical experience with the first U.S. Food and Drug Administration (FDA)-approved MIGS device, the Glaukos iStent Trabecular Micro-Bypass (Glaukos Corporation, San Clemente, CA), has yielded a considerable body of long-term data from protocol-guided and independent surgeon studies in patients with mild to moderate open-angle glaucoma undergoing concomitant cataract surgery,[6-13] as well as in pseudoexfoliative glaucoma, advanced glaucoma, stand-alone surgery, and multi-stent use.[14-26]

The iStent *inject* Trabecular Micro-Bypass System Model G2-M-IS (Glaukos Corporation) is the second trabecular micro-bypass device approved by the FDA. This 2-stent system creates 2 patent bypasses through the trabecular meshwork. In 2011, this device received CE Mark approval. Prior study results with this second-generation device have shown durable and safe reductions of IOP and medication burden both with[27-33] and without[34-37] concomitant cataract surgery. The described U.S. pivotal study supporting the recent FDA approval was a large randomized trial evaluating stent implantation with concomitant cataract surgery compared with cataract surgery alone in patients with mild to moderate primary open-angle glaucoma (POAG) and cataract. The present article presents safety and effectiveness outcomes through 2 years postoperatively.

Methods

Study Design and Participants

This study was a prospective, randomized, single-masked, controlled, multicenter U.S. pivotal trial investigation initiated in September 2011. The study was designed to assess the safety and effectiveness at 2 years postoperative of the second-generation trabecular micro-bypass stent system in patients with mild to moderate POAG and cataract. A targeted total of 500 eyes were to be randomized in a 3:1 ratio to the treatment group or control group after completion of uncomplicated cataract surgery. The randomization scheme was based on a computer-generated list. After surgery, subjects and the technicians performing postoperative measurements were masked to treatment assignment for the duration of study follow-up.

The primary effectiveness end point was a $\geq$20% reduction from baseline in diurnal IOP (DIOP) without ocular hypotensive medication at month 24. The secondary effectiveness end point was the 24-month DIOP reduction from baseline without medication. Eyes with secondary surgical interventions to lower IOP or other events (including loss of light perception or hypotony (IOP <6 mmHg) associated with clinically significant findings) were considered nonresponders. Safety measures included best spectacle-corrected visual acuity (BSCVA), slit-lamp and fundus examinations, gonioscopy, pachymetry, specular microscopy, visual field testing, adverse events (AEs), and complications.

The key elements of the study design are in alignment with the FDA Guidance on Premarket Studies of Implantable Minimally Invasive Glaucoma Devices (December 2015) and the ANSI Z80.27-2014 Standard for Implantable Glaucoma Devices. The study was conducted with Institutional Review Board approval, and study procedures followed the tenets of the Declaration of Helsinki (2008), including written informed consent of all participating subjects. The study was registered with the National Library of Medicine (clinicaltrials.gov, NCT00323284).

Inclusion and Exclusion Criteria

Inclusion criteria included the following: (1) diagnosis of mild to moderate POAG; (2) age-related cataract eligible for phacoemulsification, with BSCVA 20/40 or worse in the presence of glare; (3) screening IOP $\leq$24 mmHg while on 1 to 3 ocular hypotensive medications, with a stable medication regimen for $\geq$2 months; (4) baseline unmedicated (post-washout) DIOP $\geq$21 mmHg and $\leq$ 36 mmHg, and at least 3 mmHg higher than medicated screening IOP; (5) screening cup-to-disc (C:D) ratio of 0.8 or less; (6) normal open-angle anatomy (Shaffer grade $\geq$3) by gonioscopy; and (7) ability to provide an adequate, interpretable visual field. A diagnosis of mild to moderate POAG required glaucomatous visual field defects (with mean deviation [MD] not worse than -12 decibels [dB]) or nerve abnormality characteristic of glaucoma (including 1 or more of the following: segmental loss of neuroretinal rim (notching), disc hemorrhage, pseudo pit of the disc, nerve fiber layer loss, visible laminar dots).

Exclusion criteria included (1) traumatic, uveitic, neovascular, or angle-closure glaucoma, or glaucoma associated with vascular disorders; (2) history of incisional glaucoma surgery, argon laser trabeculoplasty, iridectomy, or iridotomy, or completion of selective laser trabeculoplasty (SLT) within 90 days before screening; (3) visual field MD worse than -12 dB; (4) ocular disease affecting safety or eligibility for washout; (5) any corneal, lenticular, choroidal, retinal, or other ocular or systemic condition that would preclude safe surgery or follow-up examinations; (6) fellow eye BSCVA worse than 20/80; (7) functionally significant visual field loss, including severe nerve fiber bundle defects such as Bjerrum scotoma; and (8) visual field status that would be placed at risk by the washout period.

Postoperative Medications and Follow-up

In both groups, ocular medications after surgery included 1 week of topical antibiotics and 4 weeks of tapered topical prednisolone acetate 1%. After 1 month postoperatively, ocular hypotensive medication was to be reintroduced if IOP exceeded 18 mmHg at 2 consecutive times within 3 days. Investigators were instructed to reintroduce the same medication as the subjects' preoperative regimen, if possible. Postoperative study visits occurred at 6 hours, day 1, week 1, and months 1, 3, 6, 11, 12, 18, 23, and 24. At the month 11 and 23 visits, subjects using ocular hypotensive medication(s) were instructed to undergo medication washout to permit unmedicated DIOP assessment at months 12 and 24, respectively. If subjects could not be washed out because of safety issues, this was noted by the investigator.

Assessment of Intraocular Pressure

All IOP measurements were by Goldmann applanation per standard clinical practice for glaucoma studies, using a 2-person method (1 to look through the slit lamp and turn the dial, and 1 to record the IOP reading).[38] The DIOP was calculated as the mean of 3 individual IOP measurements on the same day (at approximately 8:00 AM, 12:00 PM, and 4:00 PM). The DIOP measurements were performed at the baseline visit and at months

6, 12, and 24. The baseline visit occurred after a preoperative medication washout was completed, according to a defined washout period (a minimum of 5 days for carbonic anhydrase inhibitors, 2 weeks for alpha adrenergic agonists, and 4 weeks for β-blockers, prostaglandin analogs, combination products, and pilocarpine).

Study Device

The iStent *inject* is designed to create a pathway through the trabecular meshwork into Schlemm's canal to facilitate aqueous outflow, thereby decreasing IOP. Each injector is preloaded with 2 titanium stents, each having 230 μm diameter, 360 μm height, 80 μm central lumen diameter, and four 50-μm side outlets to allow for multidirectional outflow (Figs 1 and 2). Each stent is designed to carry the total amount of aqueous humor produced (average 2.5 μl/min) by the human body. The *ab interno* multiple stent placement is designed to increase access to more collector channels.

Stent Implantation

Implantation of the device was completed as follows. Intracameral miotic or viscoelastic was used to deepen the angle and maintain the anterior chamber. The injector was advanced under direct gonioscopy through the existing corneal incision to the nasal trabecular meshwork, where the first stent was implanted into Schlemm's canal. Without withdrawing from the eye, the injector tip then was repositioned laterally to implant the second stent approximately 2 to 3 clock hours away from the first stent. Proper stent placement and seating were confirmed after implantation. At the completion of the procedure, viscoelastic was removed and proper sealing of the corneal incision was ensured.

Statistical Analyses

Effectiveness end points were analyzed within the Effectiveness Cohort, consisting of subjects who were randomized to the treatment group and received 2 stents, or who were randomized to the control group, according to the randomly assigned treatment.

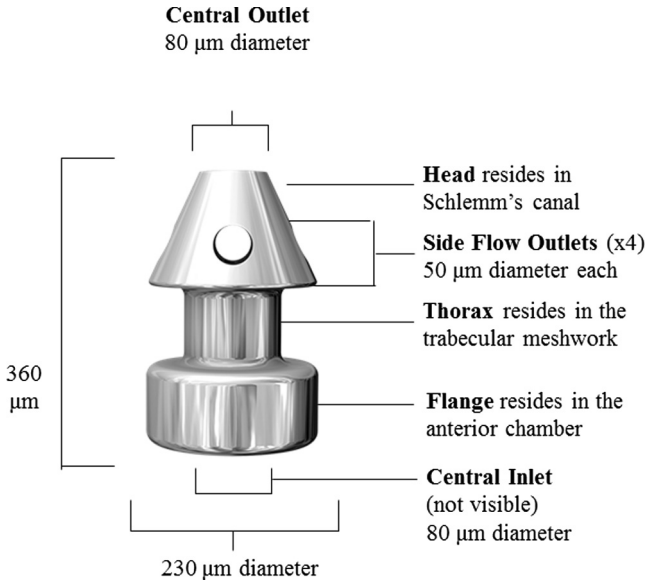

Figure 1. iStent *inject* GTS 400 (Glaukos Corporation, San Clemente, CA) stent design and dimensions.

Effectiveness outcomes also were analyzed for the intent-to-treat cohort, consisting of all randomized subjects. Safety outcomes were assessed within the Safety Population, which consisted of all randomized subjects, with analysis based on the treatment actually received. The primary effectiveness end point was compared between the 2 study groups using the Fisher exact test. The 2-sample *t* test was used to compare the 2 groups with respect to the secondary effectiveness end point and the reduction in ocular hypotensive medications. Statistical significance was demonstrated if the 2-sided *P* value was < 0.050. The necessary sample size was calculated as 376 eyes (282 treatment and 94 control) for the primary effectiveness outcome. To support safety analyses requiring at least 300 treatment subjects, the calculated sample size was 500 eyes.

Results

Demographics and Preoperative Characteristics

A total of 505 qualified eyes were randomized to cataract surgery with stent implantation (n = 387) or cataract surgery only (n = 118) at 1 of 41 sites. The preoperative mean medicated IOP was 17.5 mmHg (standard deviation [SD], 3.0) in the treatment group and 17.5 mmHg (SD, 2.8) in the control group (Table 1). A total of 16.8% of treatment eyes and 14.4% of control eyes were receiving 3+ medications preoperatively. The preoperative mean unmedicated DIOP was 24.8 mmHg (SD, 3.3) in the treatment group and 24.5 mmHg (SD, 3.1) in the control group. A total of 23 eyes (5.9%) in the treatment group and 6 eyes (5.1%) in the control group had a history of SLT more than 90 days before screening. No significant differences between the groups' demographic or preoperative ocular characteristics were observed.

Operative Parameters

Of the 387 eyes randomized to the stent group, 380 (98.2%) were implanted with 2 stents. Four eyes (1.0%) were implanted with 3 stents, and 2 eyes (<1%) were implanted with 1 stent; in 1 of the 387 eyes, after successful cataract extraction and IOL implantation and subsequent randomization to the treatment group, stent implantation was not attempted as a result of excessive coughing (i.e., 0 stents implanted). Outcomes for the 7 treatment eyes not implanted with 2 stents are described later in this article.

In the 386 eyes implanted with stents, 11 intraoperative AEs were reported during stent implantation (2.8%). These consisted of the aforementioned 4 cases of 3 stents being implanted and 2 cases of 1 stent implanted, as well as 1 case each of 2 stents implanted in the same location and stent implanted in the ciliary body, and 3 cases of corneal abrasion that resolved by 3 days postoperatively.

Effectiveness

The primary effectiveness end point was met, with 75.8% (288/380) in the treatment group and 61.9% (73/118) in the control group achieving a clinically significant (≥20%) reduction in medication-free DIOP from baseline at 24 months. This difference between groups was statistically significant ($P = 0.005$; Fig 3). The secondary end point was also met, with mean reduction in medication-free DIOP from baseline to 24 months of 7.0 mmHg (SD, 4.0) in the treatment group compared with 5.4 mmHg (SD, 3.7) in the control group ($P < 0.001$; Fig 4).

Of the subjects who were responders (e.g., 24-month unmedicated mean DIOP reduced by ≥20% from baseline in the absence of IOP-affecting surgery during the study), 84% of treatment eyes and 67% of control group eyes were not receiving ocular hypotensive medication at 23 months. In addition, 63.2% of treatment

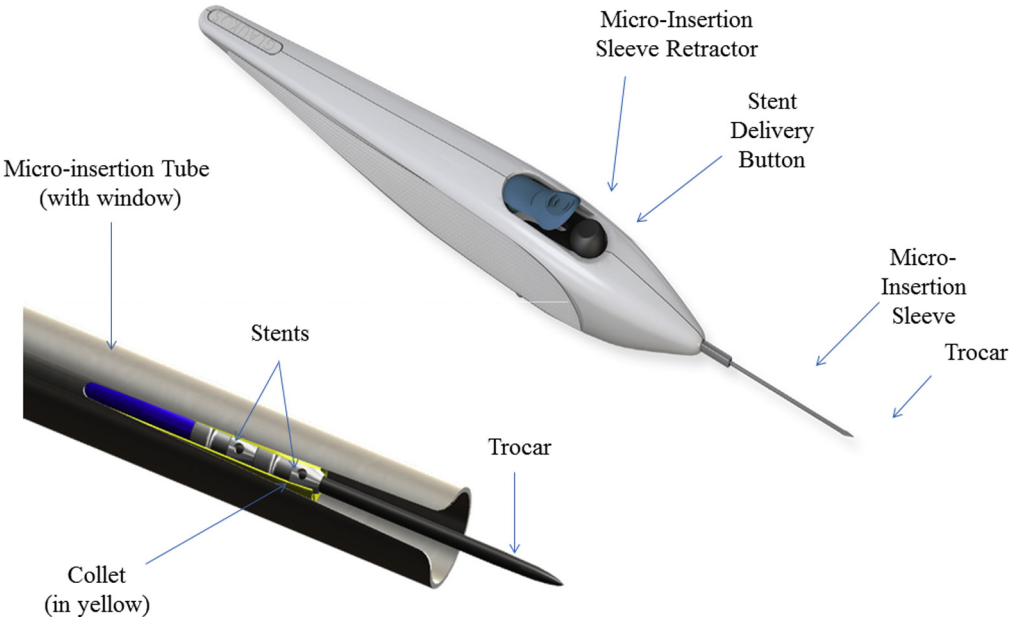

Figure 2. iStent *inject* G2-M-IS injector design.

eyes and 50.0% of control eyes had month 24 medication-free DIOP ≤18 mmHg (difference 13.2%; 95% confidence interval [CI], 2.9−23.4). In the eyes that did not undergo secondary surgical interventions to lower IOP, mean observed unmedicated DIOP at 24 months was 17.1 mmHg (SD, 3.6; 31% reduction from baseline DIOP of 24.8 mmHg) in the treatment group and 17.8 mmHg (SD, 3.5; 27% reduction from baseline DIOP of 24.5 mmHg) in the control group. At month 24 (a protocol-specified washout visit), a small portion of the overall sample (12 subjects in the treatment group and 6 subjects in the control group) did not undergo washout.

Among medication-free eyes, the mean observed IOP from 6 to 24 months ranged from 15.4 to 17.1 mmHg for the treatment group and 15.8 to 17.8 mmHg for the control group. Outcomes were similar when all eyes were considered, including both those on medication and those who were medication-free. In all eyes (regardless of medication use), the mean observed IOP ranged from 15.5 to 17.2 mmHg for the treatment group and 15.9 to 17.8 mmHg for the control group. For the same time points, the mean number of ocular hypotensive medications ranged from 0.3 to 0.4 in the treatment group and 0.6 to 0.8 in the control group. Additional information on medication is provided next. Observed data at both 6 months and 12 months postoperatively show that higher proportions of subjects in the treatment group did not use ocular hypotensive medications or undergo additional IOP-lowering procedures and had greater IOP reduction from baseline compared with the control group. At 6 months, 81.4% of treatment subjects versus 64.1% required no additional medications or surgeries; in these subjects, mean IOP reduction was 9.2 mmHg in the treatment group and 8.2 mmHg in the control group. After a protocol-specified medication washout at 12 months, 97.5% of treatment subjects versus 92.2% control subjects were medication-free and did not require additional surgeries. Mean IOP reduction without medication or additional IOP-lowering surgeries at this visit was 8.5 mmHg in the treatment group and 7.5 mmHg in the control group. At both the 6- and 12-month time points, the mean observed IOP reduction was 1.0 mmHg greater in the treatment group compared with the control group. Notably, this difference in observed IOP reduction increased at 24 months favoring the treatment group by 1.3 mmHg.

In the treatment group, the mean number of ocular hypotensive medications was 1.6 (SD, 0.8) preoperatively and 0.4 (SD, 0.8) at 23 months, a mean reduction of 1.2 medications (SD, 1.0; $P < 0.001$). In the control group, the mean number of ocular hypotensive medications was 1.5 (SD, 0.7) preoperatively and 0.8 (SD, 1.0) at 23 months, a mean reduction of 0.8 medication (SD, 1.0; $P < 0.001$; difference in change between groups = 0.4 medications, $P < 0.001$).

Outcomes for Treatment Eyes Not Implanted with 2 Stents

Outcomes for the 7 treatment eyes not implanted with 2 stents were favorable, including final BSCVA of 20/25 or better in all eyes, no unanticipated AEs, no secondary glaucoma surgeries, and last reported IOP of 18 mmHg or less in 5 of 7 eyes. Three eyes met the primary end point, including 1 eye with 3 stents, 1 eye with 1 stent, and 1 eye with no stents. One subject (implanted with 3 stents) had unmedicated IOP reduction of 30% at month 23, but did not return for the month 24 exam. Two subjects (a 3-stent subject and a 1-stent subject) were not washed out of medication at 24 months (with month 24 medicated IOP of 13.0 mmHg and 15.2 mmHg, respectively), and 1 subject (implanted with 3 stents) had month 24 unmedicated IOP reduction less than 20%. Within the intent-to-treat cohort (which includes these 7 eyes not implanted with 2 stents), 75.2% of treatment eyes and 61.9% of control eyes achieved ≥20% reduction in medication-free DIOP at 24 months ($P = 0.007$); mean reduction in medication-free DIOP from baseline to 24 months was 6.9 mmHg (SD, 4.0) in the treatment group and 5.4 mmHg (SD, 3.7) in the control group ($P < 0.001$).

Safety

The majority of eyes in both groups achieved BSCVA of 20/40 or better at month 24 (98.9% of eyes in the treatment group and 98.2% of eyes in the control group). Visual field MD was stable over time (mean change close to zero) from screening to 24 months in both groups. A comparable proportion of eyes in each group (~70%) had less than a ±2.5 dB change in MD compared with

Table 1. Demographics and Preoperative Characteristics of Intent-to-Treat Population

Parameter	Cataract Surgery with iStent *inject* (Glaukos Corporation, San Clemente, CA) N=387		Cataract Surgery Only N=118
Age (yrs)			
Mean	69.0		70.1
SD	8.2		7.7
P value†		0.164	
Gender			
Male	162/387 (41.9%)		54/118 (45.8%)
Female	225/387 (58.1%)		64/118 (54.2%)
P value‡		0.459	
Race/ethnicity			
White	282/387 (72.9%)		86/118 (72.9%)
Hispanic/Latino	24/387 (6.2%)		10/118 (8.5%)
Black	77/387 (19.9%)		19/118 (16.1%)
Asian	3/387 (0.8%)		1/118 (0.8%)
American Indian	1/387 (0.3%)		0/118 (0.0%)
East Indian	0/387 (0.0%)		1/118 (0.8%)
Portuguese	0/387 (0.0%)		1/118 (0.8%)
P value‡		0.221	
Study eye			
OD	205/387 (53.0%)		64/118 (54.2%)
OS	182/387 (47.0%)		54/118 (45.8%)
P value‡		0.834	
No. of ocular hypotensive medications at screening			
1	224/387 (57.9%)		71/118 (60.2%)
2	98/387 (25.3%)		30/118 (25.4%)
3	63/387 (16.3%)		17/118 (14.4%)
4	2/387 (0.5%)		0/118 (0.0%)
P value‡		0.943	
Medicated IOP at screening (mmHg)			
Mean	17.54		17.54
SD	2.99		2.78
P value†		0.997	
Unmedicated IOP at baseline (after medication washout) (mmHg)			
Mean	24.83		24.50
SD	3.34		3.08
P value†		0.328	
BSCVA at baseline			
Mean logMAR (Snellen)	0.234 (20/34)		0.234 (20/34)
SD	0.168		0.166
P value†		0.901	
Visual field MD at screening (dB)			
Mean	−3.4		−3.4
SD	3.3		3.1
P value†		0.915	
Visual field pattern SD at screening (dB)*			
Mean	3.5		3.3
SD	2.5		2.6
Central corneal thickness at screening (μm)			
Mean	546.5		546.1
SD	36.2		35.7
P value†		0.909	
Shaffer angle grade at screening			
III (25–35)	142/387 (36.7%)		40/118 (33.9%)
IV (>35)	245/387 (63.3%)		78/118 (66.1%)
P value‡		0.661	
Vertical C:D ratio at screening*			
Mean	0.61		0.59
SD	0.16		0.18

Oral medications count as 1 medication. Combination medications count as 2 medications.
BSCVA = best spectacle-corrected visual acuity; C:D = cup-to-disc; dB = decibels; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation; OD = right eye; OS = left eye; SD = standard deviation.
*Values listed are for Safety Population.
†Two-sample *t* test.
‡Fisher exact test.

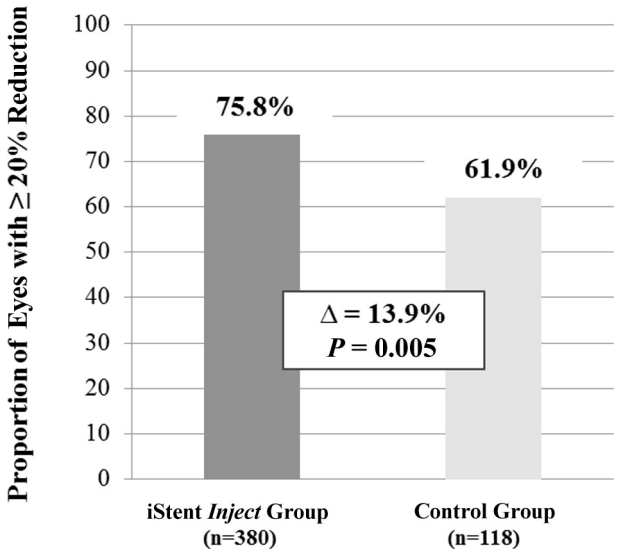

Figure 3. Primary effectiveness end point: Proportion of eyes with ≥20% reduction in medication-free diurnal intraocular pressure (DIOP) at month 24 effectiveness.

screening; an AE of MD worsening of ≥2.5 dB was reported in 1.0% of iStent *inject* eyes versus 0.8% of control eyes at the month 24 visit. Mean C:D ratio also was stable over time from screening to month 24 in both groups. Approximately 79% of eyes in both groups exhibited no change in C:D ratio at month 24 versus screening, and similar proportions of eyes had an increase of 0.3 or less in C:D ratio at 24 months versus screening (13.2% vs. 13.8% in treatment and control groups, respectively). No eye had an increase of more than 0.3 in C:D ratio.

A lower proportion of treatment eyes than control eyes experienced postoperative ocular AEs (54.1% vs. 62.2%, respectively). Adverse events occurring at a rate of 2% or greater are provided in Table 2. There were no unanticipated AEs during the study. There were no reports of hypotony at 1 month postoperatively or later, hypotony maculopathy, flat anterior chamber with lens cornea touch, shallow anterior chamber with iridocorneal apposition, wound dehiscence, endophthalmitis, corneal decompensation, choroidal hemorrhage or effusion, aqueous misdirection, cyclodialysis, atrophy/phthisis, C:D ratio increase of ≥0.3, loss of light perception, pupillary block, or hypopyon. There were no cases of stent migration or stent dislocation. There were no reports of significant hyphema (i.e., ≥10% of the anterior chamber). Microhyphemas were reported as clinical findings, not AEs, in 3.9% (n = 15) of eyes. Of the 24 total eyes with stent obstruction, only 3 underwent laser procedures to treat the obstruction, all of which were successful. Focal goniosynechiae (synonymous with peripheral anterior synechiae [PAS]) was reported as an AE in 1.8% of treatment eyes. Secondary ocular surgeries during the course of the study to achieve further IOP reduction occurred in 1.6% of treatment eyes (n = 6) and 3.4% (n = 4) of eyes in the control group. These included 2 cases of SLT and 4 cases of trabeculectomy/express shunt implantation in the treatment group, and 3 cases of SLT and 1 case of trabeculectomy/express shunt implantation in the control group (Table S3, available at www.aaojournal.org).

There was little difference in endothelial cell loss (ECL) between the treatment and control groups. Results were consistent with previous reports of cataract surgery-related ECL. The mean percent change in endothelial cell density (ECD) from preoperative to 24 months was −13.1% (SD, 12.4; 95% CI, −14.4 to −11.8) for the treatment group and −12.3% (SD, 12.7%; 95% CI, −14.8 to −9.8) for the control group. The percentage of eyes with an ECL >30% at the 24-month visit was similar between the 2 groups (10.4% in the iStent *inject* group vs. 9.5% in the control group). In both study groups, the most substantial decline in ECD occurred within the first 3 months postoperatively (12.5% in the iStent *inject* group and 11.6% in the control group), and the rate of decline was minimal thereafter.

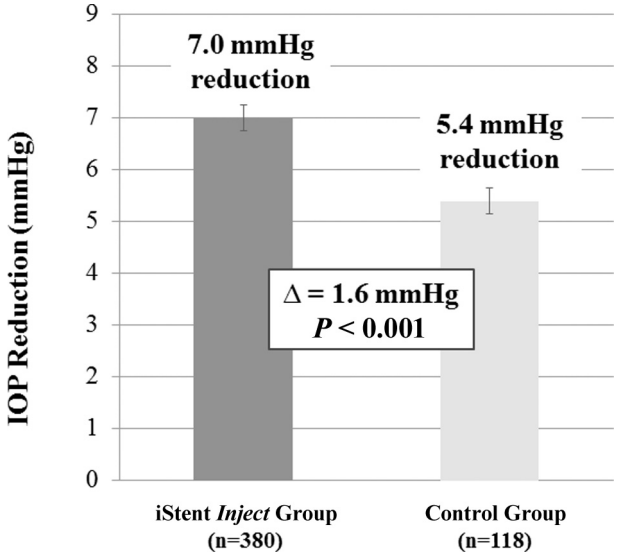

Figure 4. Secondary effectiveness end point: mean reduction in medication-free DIOP at month 24 effectiveness cohort. Vertical error bars represent standard error (0.21 in iStent *inject* group, 0.34 in control group). IOP = intraocular pressure.

Discussion

This pivotal study of the iStent *inject* second-generation trabecular micro-bypass device demonstrated significant and sustained clinical benefit, accompanied by favorable long-term safety, of stent implantation in conjunction with cataract surgery in subjects with mild to moderate POAG. The trial met the primary and secondary effectiveness end points at month 24, with clinically and statistically significant treatment effects favoring treatment eyes for both measures. The primary effectiveness outcome, achievement of ≥20% reduction in 24-month DIOP, is widely recognized as clinically significant,[39] and thus is a frequent minimum therapeutic target for patients earlier in the disease process. The proportion of eyes achieving IOP ≤18 mmHg without medication is an important additional outcome. Regarding this parameter, the study showed the clinically and statistically clinical benefit of subjects implanted with stents, in that a higher proportion of treatment eyes met this 18-mmHg threshold without the need for medication. The study outcome for the secondary end point, a 1.6-mmHg greater mean reduction in medication-free DIOP in treatment versus control eyes, is also meaningful, given the findings of prior landmark glaucoma trials that demonstrated reduced risk of visual

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

Postoperative Events	Cataract Surgery with iStent *inject* N=386 n (%)	Cataract Surgery Only N=119 n (%)	Difference in % 95% CI*
Ocular surface disease	62 (16.1%)	20 (16.8%)	−0.7% (−8.6% to 7.1%)
Stent obstruction, partial or complete, regardless of how long the obstruction is present*	24 (6.2%)	NA	
Any intraocular inflammation (not preexisting) remaining or arising after the protocol's specified medication regimen is complete†	22 (5.7%)	5 (4.2%)	1.5% (−2.8% to 5.8%)
Secondary surgical intervention‡	21 (5.4%)	6 (5.0%)	−0.4% (−4.2% to 5.0%)
Ocular allergies	11 (2.8%)	4 (3.4%)	−0.5% (−4.2% to 3.1%)
Loss of BSCVA of ≥2 lines (≥10 letters on ETDRS chart) at or after 3 mos postoperatively	10 (2.6%)	5 (4.2%)	−1.6% (−5.6% to 2.3%)
Posterior vitreous detachment	10 (2.6%)	5 (4.2%)	−1.6% (−5.6% to 2.3%)
Foreign body sensation	9 (2.3%)	0 (0.0%)	2.3% (0.8%–3.8%)
Blurred vision/visual disturbance	9 (2.3%)	2 (1.7%)	0.7% (−2.1% to 3.4%)
Extraocular inflammation	9 (2.3%)	2 (1.7%)	0.7% (−2.1% to 3.4%)
Epiretinal membrane	9 (2.3%)	3 (2.5%)	−0.2% (−3.4% to 3.0%)
IOP increase ≥10 mmHg vs. baseline IOP occurring at month ≥1§	8 (2.1%)	1 (0.8%)	1.2% (−0.9% to 3.4%)
Perioperative ocular pain within 14 days of surgery	8 (2.1%)	1 (0.8%)	1.2% (−0.9% to 3.4%)
Vitreous floaters	8 (2.1%)	3 (2.5%)	−0.4% (−3.6% to 2.7%)
Corneal abrasion	8 (2.1%)	4 (3.4%)	−1.3% (−4.8% to 2.3%)
Corneal opacity	4 (1.0%)	3 (2.5%)	−1.5% (−4.5% to 1.5%)
Hyperemia	3 (0.8%)	7 (5.9%)	−5.1% (−9.4% to −0.8%)
Nonproliferative diabetic retinopathy	2 (0.5%)	3 (2.5%)	−2.0% (−4.9% to 0.9%)
IOP increase requiring management with oral or intravenous medications or with surgical intervention at month ≥1§	1 (0.3%)	3 (2.5%)	−2.3% (−5.1% to 0.6%)

BSCVA = best spectacle-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; NA = not available.
The counts (n) are the number of subjects reported with the corresponding events. % = n ÷ N × 100%.
There were no cases of iridodialysis or significant hyphema (≥10% of anterior chamber).
*In certain cases of stent obstruction, the investigators reported associated findings of transient hyphema (n = 8), inferior pigment (n = 14), or focal goniosynechiae (n = 10). In 8 cases, investigators reported obstruction of both stents. Three cases of stent obstruction were treated with laser; obstruction resolved in all 3 cases. Seventeen cases were persistent at month 24. Of these 17 cases, the primary effectiveness end point was met in 9 cases despite no treatment with laser.
†Three subjects in the iStent *inject* group had chronic iritis defined as anterior cells or flare of grade 1+ or worse persisting for more than 3 months postoperatively that recurs less than 3 months after discontinuing the initial postoperative steroid regimen.
‡The events of "glaucoma progression requiring secondary surgical intervention" (4 iStent *inject* and 1 cataract) and "medication intolerance requiring surgical intervention" (1 iStent *inject* and 0 cataract) were included.
§The events of IOP increase requiring management with oral or intravenous medications or with surgical intervention at month ≥1 and IOP increase ≥10 mmHg versus baseline IOP occurring at month ≥1 were mutually exclusive. The events of IOP increase requiring surgical intervention occurring at month ≥1 were also included in the reports of "Secondary Surgical Intervention."

field decline with IOP reduction.[3,4,40] Reporting mean change in IOP is a relevant measure because it takes into consideration differences in baseline values between groups. Therefore, the greater IOP reduction in the treatment group and the greater proportion of treatment eyes meeting the target therapeutic goal without medication are both compelling outcomes. In addition, the IOP reduction in the treatment group at 2 years shows the long-term sustained effect of trabecular bypass with cataract surgery versus cataract surgery alone, which has been shown to lose effectiveness over time.[41]

The current study showed a mean observed DIOP of 17.1 mmHg at month 24 without the use of medications or IOP-lowering surgery. This study included a medication washout step before month 24. The impact on IOP increase of medication washout in eyes with 2 stents has been reported as approximately 4 mmHg.[15,37] Furthermore, a prior report of single versus multiple stent implantation as a stand-alone treatment showed incremental benefit with multiple stents.[23] Neither a comparison of single versus multiple stents nor the stand-alone surgical procedure was in the current study design. Nevertheless, the advantage afforded by multiple stent placement, namely, greater access to collector channels due to implantation in multiple locations, is supported by the earlier reported data.[23] Finally, an independent report of iStent *inject* implantation in conjunction with cataract surgery showed a mean IOP of 14.8 mmHg on an average of 0.8 medications at 24 months.[31] Although direct comparisons are not possible between the current work and this earlier single-surgeon report, it is possible that continued U.S. surgical experience with this technology beyond the work included in this pivotal trial may show additional IOP reduction.

Although not a study end point, the use of medication before and after stent implantation in the study eye is

relevant to the overall characterization of benefit, which is primarily based on the level of IOP reduction achieved after washout. Because patient compliance is known to decrease as the number of medications increases,[42-44] and medications have drawbacks such as toxicities and costs,[45-47] the proportions of eyes on 0, 1, or ≥2 medications are especially important indicators of treatment utility. In this study, 84% of treatment eyes meeting the primary study end point were not taking ocular hypotensive medications at 23 months, compared with 67% of control eyes.

The overall safety profile of the device was highly favorable. Excellent visual acuity was observed in both groups through 24 months. The overall rate of AEs was essentially comparable between groups and considered representative of complications that occur in a similarly aged glaucoma population undergoing cataract surgery. Typical concerns in angle-based surgery include hypotony and goniosynechiae (i.e., PAS). In this study there were no AEs of hypotony and a very low rate (<2%) of PAS. The reports of stent obstruction are consistent with prior reported rates of trabecular micro-bypass stents[6] and did not result in additional clinical sequelae. By design, the implantation of the microscopic trabecular micro-bypass stents is less invasive than larger glaucoma devices. Although IOP reduction was more modest than that of filtering surgeries required for more advanced glaucoma, there were no complications of the kind seen with filtering surgeries, such as endophthalmitis, hypotony, bleb infections, bleb leaks, and subconjunctival fibrosis.[5,48-56]

Regarding ECD, ECL rates were similar between the study groups and were consistent with those expected for cataract surgery. Mean change in ECD in both groups was well within the range and consistent with the pattern described in the literature after phacoemulsification cataract extraction. The expected change in ECD after phacoemulsification cataract extraction is described by a greater decline in the early postoperative period followed by a slow, chronic decline thereafter.[57] Consistent with the literature, in both study groups, the most substantial ECD decline occurred within the first 3 months postoperatively, and the rate of decline was minimal thereafter.

The favorable safety profile shown in this study is consistent with the high safety profile demonstrated with both versions of the trabecular micro-bypass stents (iStent and iStent *inject*). The iStent has been commercially available for more than a decade and has been available in the United States since 2012. More than 450 000 iStent devices have been distributed worldwide. Since commercial introduction of the iStent *inject* in 2011, more than 45 000 iStent *inject* devices have been distributed worldwide to date. The rate of reportable intraoperative or postoperative findings with either product is less than 0.1%. The rate of stent removals is 0.007%. There have been no product recalls, field safety notices, or product withdrawals of either the iStent or iStent *inject*. The significant body of postmarket experience worldwide with iStent, and outside the United States with iStent *inject,* represents a highly favorable device safety profile and supports the safety results observed in the pivotal trials.[58]

The main study limitations were that surgeons were not masked to the treatment groups, and the data include the surgeons' learning curve with the technology. Despite these factors, the study provides meaningful information and portrays the clinically and statistically significant treatment effect of stent implantation.

This randomized pivotal trial demonstrates the effectiveness and safety of implanting iStent *inject* second-generation trabecular micro-bypass stents in conjunction with cataract surgery in patients with mild to moderate POAG and cataract. Given established expectations of excellent visual improvement with low complications after cataract surgery, it is noteworthy that the greater unmedicated IOP reduction after stent implantation was accomplished while maintaining overall favorable safety similar to that of cataract surgery through 2 years postoperative. Consistent with other MIGS pivotal randomized controlled trials,[6,59-61] meaningful IOP reduction was observed in this study's control group of cataract surgery alone. However, the additional IOP reduction observed in the treatment group supports the strategy that glaucoma surgery performed coincident to cataract surgery be minimally disruptive and mechanistically synergistic so that the favorable effect of phacoemulsification is not adversely affected. This micro-invasive glaucoma intervention lowers IOP to a greater degree than cataract surgery alone, while postponing or possibly eliminating the need for more invasive glaucoma treatment. Any additional IOP reduction supports the ultimate goal of slowing disease progression and preserving vision. Thus, the study's findings support the consideration of iStent *inject* second generation trabecular micro-bypass stent implantation as a safe, durable, and less compliance-dependent treatment modality for additional unmedicated IOP reduction in POAG eyes undergoing cataract surgery.

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HUMAN SUBJECTS: Human subjects were included in this study. The key elements of the study design are in alignment with the FDA Guidance on Premarket Studies of Implantable Minimally Invasive Glaucoma Devices (December 2015) and the ANSI Z80.27-2014 Standard for Implantable Glaucoma Devices. The study was conducted with Institutional Review Board (IRB) approval, and study procedures followed the tenets of the Declaration of Helsinki (2008), including written informed consent of all participating subjects.

No animal subjects were used in this study.

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Abbreviations and Acronyms:
AE = adverse event; **BSCVA** = best spectacle-corrected visual acuity; **C:D** = cup-to-disc; **CE** = Conformité Européenne; **CI** = confidence interval; **dB** = decibels; **DIOP** = diurnal intraocular pressure; **ECD** = endothelial cell density; **ECL** = endothelial cell loss; **FDA** = Food and Drug Administration; **IOP** = intraocular pressure; **MD** = mean deviation; **MIGS** = micro-invasive glaucoma surgery; **PAS** = peripheral anterior synechiae; **POAG** = primary open-angle glaucoma; **SD** = standard deviation; **SLT** = selective laser trabeculoplasty.

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