

Prospective Evaluation of Two iStent[®] Trabecular Stents, One iStent Supra[®] Suprachoroidal Stent, and Postoperative Prostaglandin in Refractory Glaucoma: 4-year Outcomes

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Received: November 2, 2017 / Published online: February 23, 2018
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ABSTRACT

Introduction: This study evaluates long-term outcomes of two trabecular micro-bypass stents, one suprachoroidal stent, and postoperative prostaglandin in eyes with refractory open angle glaucoma (OAG).

Methods: Prospective ongoing 5-year study of 80 eligible subjects (70 with 4-year follow-up) with OAG and IOP \geq 18 mmHg after prior

trabeculectomy and while taking 1–3 glaucoma medications. Subjects received two iStent[®] trabecular micro-bypass stents, one iStent Supra[®] suprachoroidal stent, and postoperative travoprost. Postoperative IOP was measured with medication and annually following medication washouts. Performance was measured by the proportion of eyes with \geq 20% IOP reduction on one medication (the protocol-specified prostaglandin) versus preoperative medicated IOP (primary outcome); and the proportion of eyes with postoperative IOP \leq 15 and \leq 18 mmHg on one medication (secondary outcome). Additional clinical and safety data included medications, visual field, pachymetry, gonioscopy, adverse events, visual acuity, and slit-lamp and fundus examinations.

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Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s12325-018-0666-4>) contains supplementary material, which is available to authorized users.

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Results: Preoperatively, mean medicated IOP was 22.0 ± 3.1 mmHg on 1.2 ± 0.4 medications, and mean unmedicated IOP was 26.4 ± 2.4 mmHg. Postoperatively, among eyes without later cataract surgery, mean medicated IOP at all visits through 48 months was ≤ 13.7 mmHg ($\geq 37\%$ reduction), and annual unmedicated IOP was ≤ 18.4 mmHg (reductions of $\geq 30\%$ vs. preoperative unmedicated IOP and $\geq 16\%$ vs. preoperative medicated IOP). At all postoperative visits among eyes without additional surgery or medication, $\geq 91\%$ of eyes had $\geq 20\%$ IOP reduction on one medication versus preoperative medicated IOP. At month 48, 97 and 98% of eyes achieved IOP ≤ 15 and ≤ 18 mmHg, respectively, on one medication. Six eyes required additional medication, no eyes required additional glaucoma surgery, and safety measurements were favorable throughout follow-up.

Conclusion: IOP control was achieved safely with two trabecular micro-bypass stents, one suprachoroidal stent, and postoperative prostaglandin. This microinvasive, ab interno approach introduces a possible new treatment option for refractory disease.

Trial Registration: NCT01456390.

Funding: Glaukos Corporation.

Keywords: Glaucoma; iStent; iStent Supra; Microinvasive glaucoma surgery (MIGS); Ophthalmology; Prostaglandin; Refractory glaucoma; Suprachoroidal; Trabecular

INTRODUCTION

Glaucoma is a leading cause of blindness worldwide, and its management requires persistent lifelong therapy. Within the United States, primary open angle glaucoma (OAG) affects approximately 2.71 million people and is the cause of legal blindness in 5.2% of Caucasian and 18.8% of African American individuals [1, 2]. The therapeutic goal of various treatments—such as topical medications, laser procedures, microinvasive glaucoma surgery (MIGS), or traditional filtering surgery—is to reduce intraocular pressure (IOP) in order to prevent damage to the optic nerve. Over the

past decade, MIGS procedures with implantation of trabecular micro-bypass stents have reduced IOP by connecting the anterior chamber with Schlemm's canal, thereby bypassing the damaged trabecular meshwork. Numerous studies have assessed outcomes for up to 5 years following implantation of the first FDA-approved trabecular micro-bypass device, the iStent® Trabecular Micro-Bypass (Glaukos, San Clemente, CA, USA). These data have demonstrated that implanting single [3–10] or multiple [11–15] first-generation iStent devices, either with or without cataract surgery, can provide long-term IOP and medication reduction in patients with mild to moderate glaucoma. In addition, more recent studies have reported similarly positive outcomes with second-generation iStent *inject*® Trabecular Micro-Bypass devices (Glaukos) implanted with cataract surgery or in a sole procedure [16–20]. Furthermore, MIGS procedures with these stents have demonstrated a favorable risk profile when compared with that of traditional filtering surgeries [21–24].

Until now, trabecular micro-bypass stents have been used primarily for mild to moderate OAG. Meanwhile, for more severe OAG, including refractory cases, treatments have typically involved incisional glaucoma surgeries such as trabeculectomy or tube shunts, with attendant immediate and long-term risks of sequelae such as endophthalmitis, hypotony, bleb leaks, fibrosis, and bleb infections [21–30]. In more recent years, however, emerging literature has pointed to the potential utility of trabecular micro-bypass stents for these more advanced glaucoma cases [7, 8, 31–33]. Going one step further, some recent studies have examined the effect of simultaneously increasing two forms of outflow via two proven treatment modalities (conventional outflow via trabecular micro-bypass, and both uveoscleral and conventional outflow via a prostaglandin analogue) [15, 20, 34]. In two such studies by the MIGS Study Group, substantial IOP and medication reductions were demonstrated through 36 months following treatment with two trabecular stents (either iStent [15, 34] or iStent *inject* [20]) together with postoperative daily travoprost in eyes with OAG not

controlled on two ocular hypotensive medications. These data have suggested that reduced IOP and medication burden may be achieved by a minimally invasive approach.

Building upon these studies of the dual-outflow, dual-modality concept to facilitate both trabecular and uveoscleral outflow, the present study examined the utility of further bolstering uveoscleral outflow via a third modality, the iStent Supra suprachoroidal stent (Glaukos). Specifically, we evaluated outcomes through 4 years following treatment with two iStent trabecular micro-bypass stents, one iStent Supra suprachoroidal stent, and daily postoperative prostaglandin in eyes with refractory OAG (defined as eyes with history of prior incisional glaucoma surgery and with uncontrolled IOP on one to three medications). Earlier reports from this study showed that this treatment strategy could reduce mean IOP by 30–40% in these eyes, with a favorable safety profile [35–38].

With the limited choices available for treatment of refractory glaucoma, finding alternate approaches to prevent vision loss, particularly approaches with less collateral ocular tissue damage and lower complication rates, is a valuable goal of the ophthalmology community. Since MIGS with ab interno glaucoma devices potentially could meet these requirements, the present report contributes needed data on the role of MIGS within this refractory setting. This study tests the hypothesis that treatment with two trabecular micro-bypass stents, one suprachoroidal stent, and postoperative prostaglandin is able to safely produce long-term IOP and medication reductions in post-trabeculectomy refractory glaucoma cases.

METHODS

Study Design

This study was a prospective, single-arm, open-label study of the safety and utility of a new treatment approach for refractory glaucoma. The treatment included the implantation of two iStents (Glaukos) and one iStent Supra (Glaukos), and a daily postoperative prostaglandin,

travoprost. For the purposes of the study, refractory glaucoma was defined as uncontrolled IOP despite prior trabeculectomy or tube shunt surgery and treatment with one to three ocular hypotensive medications; this definition is consistent with the American National Standard for Ophthalmic Glaucoma Devices [39].

A total of 14 visiting MIGS Study Group surgeons from six countries (US, Canada, UK, Germany, Spain, Italy) and one staff surgeon (Armenia) participated in the study. All surgeons were trained on surgical technique for iStent and iStent Supra implantation and on the study protocol. All surgeries and follow-up visits were completed at the S.V. Malayan Ophthalmological Center in Yerevan, Armenia, and Ethics Committee approval was provided by the Armenian Ministry of Health. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Armenian Ministry of Health) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study. The study registration number is NCT01456390 (ClinicalTrials.gov).

The study was designed to enroll 80 eyes of 80 phakic or pseudophakic subjects with OAG (including pseudoexfoliative), history of filtering surgery (trabeculectomy or tube shunt), current treatment with one to three medications, and cup-to-disc (C:D) ratio of 0.9 or less. Exclusion criteria included a history of prior trabecular stent implantation, argon laser trabeculoplasty (ALT), or refractive surgery, or a history of selective laser trabeculoplasty (SLT) within 90 days prior to screening. Subjects were also excluded if they had abnormal angle anatomy (e.g., peripheral anterior synechiae), corneal dystrophy or opacity, or best-corrected visual acuity (BCVA) worse than 20/200 in either eye. Preoperative IOP requirements included medicated IOP ≥ 18 and ≤ 45 mmHg, and unmedicated (post-washout) IOP ≥ 21 and ≤ 45 mmHg.

Performance measures assessed at each visit included IOP measured by Goldmann applanation, and ocular hypotensive medication use. Additionally, each subject completed annual 1-month washouts of medications, with

unmedicated evaluations conducted at months 13, 25, 37, and 49. Treatment effectiveness was evaluated by the proportion of eyes with $\geq 20\%$ IOP reduction on one medication (the protocol-specified prostaglandin) at 4 years versus preoperative medicated IOP (primary outcome), and the proportion of eyes with 4-year postoperative IOP ≤ 15 and ≤ 18 mmHg on one medication (secondary outcome). Proportional analyses also were performed at annual post-washout visits to determine the percentages of eyes with unmedicated IOP reduction of $\geq 20\%$ versus baseline unmedicated IOP. For continuous variables such as IOP at each visit, descriptive analyses included mean and standard deviation. IOP data from subjects who underwent cataract surgery were excluded from IOP analyses after such surgery. Subjects who underwent any additional surgery (including cataract or glaucoma surgery) were to be excluded from mean IOP calculations after such surgery. Subjects who underwent glaucoma surgery or who required more medication than just prostaglandin were considered non-responders in proportional IOP analyses. Safety assessment in all eyes included: intraoperative and postoperative adverse events; BCVA; automated visual field; pachymetry; and findings from slit-lamp, gonioscopic, and fundus (including optic nerve assessment and C:D ratio) examinations. All postoperative examinations were conducted by the staff surgeon and glaucoma-trained staff

ophthalmologists. Subject follow-up will be ongoing for 5 years.

Surgical Devices and Technique

The iStent[®] Trabecular Micro-Bypass device (Glaukos) is a single-piece, heparin-coated titanium stent that is approximately 1.0 mm in length and 0.33 mm in height with a “snorkel” bore diameter of 120 μm . The stent, shown in Fig. 1, is inserted ab internally through the nasal trabecular meshwork into Schlemm’s canal, thus creating a bypass to improve aqueous outflow via the natural physiologic pathway. In this study, a second iStent was implanted in the same manner approximately 2–3 clock hours away from the first iStent. The iStent Supra[®] (Glaukos), shown in Fig. 2, is a suprachoroidal stent made of polyethersulfone and titanium, with a heparin-coated lumen of approximately 165 μm in diameter. Following uneventful implantation of two iStent devices (as described above), the iStent Supra is positioned ab internally through the trabecular meshwork into the suprachoroidal space approximately halfway between the iStents in this study, thereby increasing aqueous outflow via the uveoscleral pathway. The iStent and iStent Supra are each pre-loaded on a single-use inserter which is advanced through a single small temporal clear



Fig. 1 iStent[®] trabecular micro-bypass



Fig. 2 iStent Supra[®] suprachoroidal micro-bypass

corneal incision, thereby preserving tissue for future glaucoma surgery should it be needed.

Following each surgical procedure, subjects were placed on topical antibiotic medication (tobramycin 0.3%) for 1 week and topical corticosteroid medication (dexamethasone 0.1%) tapered over 4 weeks. At day 1 postoperative, subjects began once-nightly topical prostaglandin (travoprost), which was continued for the duration of the study except during wash-out periods. Additional medication and/or glaucoma surgery was to be instituted if a subject’s postoperative IOP exceeded 21 mmHg and/or in the case of glaucomatous optic nerve or visual field changes.

RESULTS

IOP and Medications

A total of 80 eyes of 80 qualified subjects constituted the intent-to-treat (ITT) cohort and underwent surgery, and 70 of these subjects have completed 49 months of follow-up. Subject demographics and baseline ocular parameters of the ITT group are summarized in Table 1, and visual field measurements are shown in Table 2. In brief, mean age was 65.2 ± 12.9 years, and all subjects had a history of prior trabeculectomy. Consistent with advanced disease, the mean preoperative C:D ratio was 0.8 and average visual field mean deviation was -13 dB. Preoperative mean medicated IOP was 22.0 ± 3.1 mmHg on a mean of 1.2 ± 0.4 preoperative medications, and preoperative mean unmedicated (post-washout) IOP was 26.4 ± 2.4 mmHg. The two most common preoperative medications, either as a sole agent or combined with other ocular hypotensive agents, were beta-adrenergic antagonists (74% of eyes) and prostaglandin analogs (24% of eyes).

Postoperatively, among all eyes not undergoing additional surgery during follow-up, mean medicated IOP at all visits through 48 months was ≤ 13.7 mmHg, as presented in Fig. 3. This represents a $\geq 37\%$ mean reduction from preoperative medicated IOP. In addition, the mean unmedicated IOP at annual post-

Table 1 Subject demographics and preoperative ocular parameters

	n = 80
Age (years)	
Mean (SD)	65.2 (12.9)
Range	27–86
Gender (n)	
Male/female	34/46
Eye (n)	
OD/OS	39/41
Preop medicated IOP (mmHg)	
Mean (SD)	22.0 (3.1)
Cup-to-disc ratio	
Mean (SD)	0.8 (0.1)
Range	0.5–1.0
# Preoperative medications	
Mean (SD)	1.2 (0.4)
Preoperative medication type n (%)	
Beta-blocker	59 (74%)
Prostaglandin analogue	19 (24%)
Carbonic anhydrase inhibitor	10 (13%)
Alpha agonist	7 (9%)
BCVA (decimal)	
Mean (SD)	0.2 (0.4) ^a
Post-washout IOP (mmHg)	
Mean (SD)	26.4 (2.4)

SD standard deviation, Preop preoperative, IOP intraocular pressure, BCVA best-corrected visual acuity

^a Due to financial constraints and limited medication access, many Armenian patients may undergo glaucoma surgery at an earlier stage than is usually seen in more well-resourced settings. This predisposition toward earlier filtering surgery may help to account for the more mild level of baseline BCVA loss than typically would be expected in a refractory glaucoma population. Additionally, given that glaucoma initially affects the more peripheral visual field, it is plausible for a patient cohort to have a range of BCVA even in the setting of more advanced baseline VF mean deviation measurements. Regardless of BCVA, the advanced nature of disease is evidenced by the preoperative mean C:D ratio (0.8) as well as preoperative visual field mean deviation (-13.0 dB, as shown in Fig. 2)

washout visits ranged from 17.1 to 18.4 mmHg, equating to a 30–35% reduction from preoperative mean unmedicated IOP, and a 16–22% reduction from preoperative mean medicated IOP. Figure 4 displays the proportion of eyes with IOP reduction $\geq 20\%$ on one postoperative medication versus preoperative medicated IOP,

Table 2 Screening and month 48 cup-to-disc ratio, visual field, and central corneal thickness

	Screening	Month 48
<i>n</i>	80	70
Cup-to-disc ratio, mean (SD)	0.8 (0.1)	0.8 (0.1)
Visual field-MD (dB), mean (SD)	− 13.0 (8.6)	− 13.2 (8.5)
Visual field-PSD (dB), mean (SD)	6.0 (2.7)	5.8 (2.6)
Central corneal thickness (μm), mean (SD)	523.1 (37.9)	526.4 (33.3)

SD standard deviation, *MD* mean deviation, *PSD* pattern standard deviation

and also the proportion of eyes with $\geq 20\%$ reduction in postoperative unmedicated IOP versus preoperative unmedicated IOP. Both proportions were high throughout follow-up, ranging approximately 91–98% in the medicated comparison and 92–97% in the unmedicated comparison. The proportions of eyes with IOP on one medication ≤ 15 and ≤ 18 mmHg also remained high, and were 97 and 98%, respectively, at the month 48 visit (Fig. 5).

Additional medication (in addition to travoprost) and/or glaucoma surgery was to be instituted if a subject's postoperative IOP exceeded 21 mmHg and/or in the case of glaucomatous optic nerve or visual field changes. Given these parameters, six total eyes required additional medication by 3 months; these subjects were included in analyses of mean IOP at each visit (Fig. 3), and were considered non-responders in the proportional analyses (Figs. 4, 5). No medication was added in any other eye for the remainder of follow-up.

Safety Assessment

There was one intraoperative report of inability to implant the suprachoroidal stent due to reduced visibility; this occurred after successful implantation of two iStent devices, which remained intact and resulted in no subsequent

sequelae. Otherwise, there were no intraoperative adverse events, including no choroidal effusion, hyphema, nor iridodialysis. Postoperatively, a total of 15 adverse events occurred: 12 reports of ≥ 3 line drop in BCVA, and 3 non-study-related deaths. Of the 12 eyes with reduced BCVA, 1 was due to variable vision from fluctuating visual field and 11 were due to advancing cataract (of whom 10 underwent cataract surgery and 1 had cataract surgery pending). After cataract surgery, the IOP measurements of these 10 patients were excluded from IOP analyses. Importantly, no subjects required additional glaucoma surgery during the entire 4-year follow-up period.

Postoperative measures of central corneal thickness, visual field mean deviation and pattern standard deviation, and C:D ratio remained approximately stable throughout follow-up, as shown in Table 2. BCVA from screening to month 48 also appeared generally stable, as presented in Fig. 6.

DISCUSSION

The treatment of refractory glaucoma presents complex challenges for surgeons and patients. Therapeutic options traditionally have included maximizing the number of medications and/or undergoing a second trabeculectomy or aqueous shunt surgery as disease advances. Medications have coexistent side effects, costs, and/or toxicities [40–42], and their effectiveness is limited by the widely-known low adherence level of patients to medical therapy [43–46]. Filtering surgery carries a lifelong risk of complications such as endophthalmitis, hypotony, bleb infections, bleb leaks, and fibrosis [21–30]. Meanwhile, iStent technology has predominantly been used in cases of mild to moderate OAG, where it has demonstrated long-term effectiveness and excellent safety [3–6, 9–20]. However, several recent reports have shown that the iStent may also be beneficial in cases of more advanced disease [7, 8, 31–33]. Given the difficulty of treating refractory disease, and the risk profile associated with more invasive traditional interventions, the present study offers

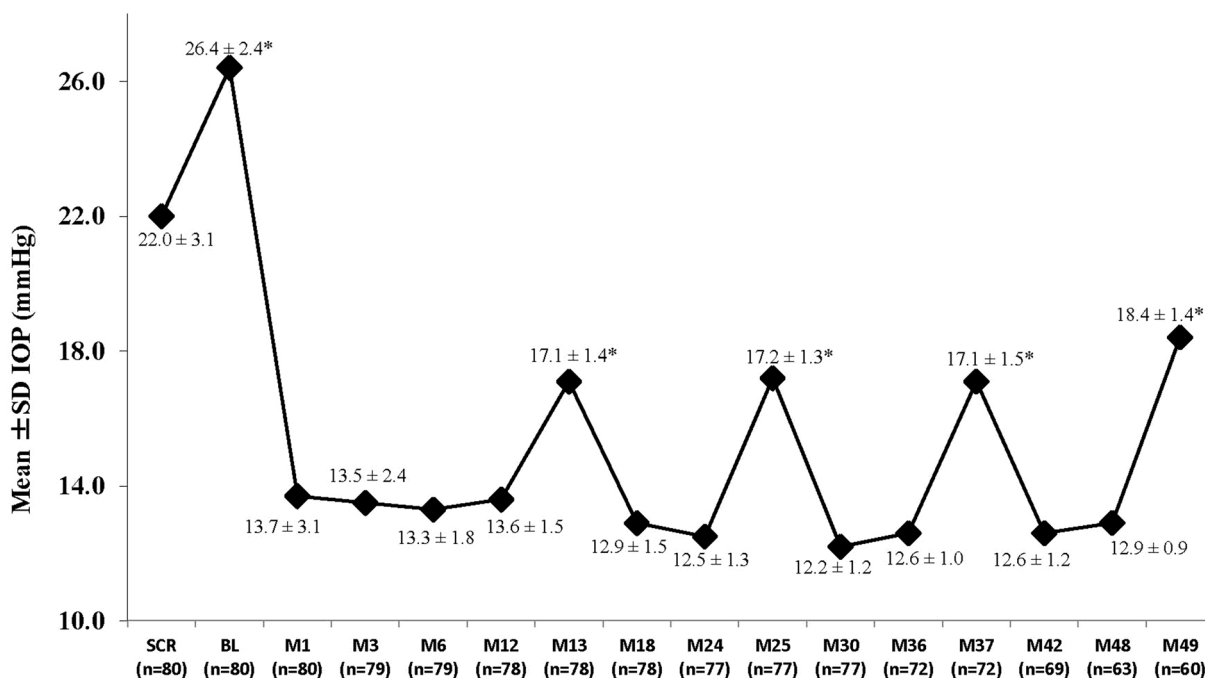


Fig. 3 Mean IOP over time. *Unmedicated IOP (at months 13, 25, 37, 49) was assessed after 1-month washout. ^aExcludes data after additional surgery (either

glaucoma surgery [*n* = 0] or cataract surgery [*n* = 10]). IOP Intraocular pressure, SD Standard deviation, SCR screening, BL baseline, M month

insight into a novel minimally invasive treatment approach for these patients.

To our knowledge, this is the first study to evaluate trabecular micro-bypass in an entirely refractory patient population; all patients had history of prior trabeculectomy and had IOP above goal despite 1–3 medications. In addition, it is the first study to introduce a treatment strategy using three treatment modalities (trabecular stent, suprachoroidal stent, and topical prostaglandin) to target both trabecular and uveoscleral outflow. In the cohort of subjects followed through 48 months, the vast majority of eyes (approximately 94–98%) achieved post-operative IOP on one medication of ≤ 18 mmHg at all visits, which is clinically significant, given that visual field progression is delayed when IOP consistently is maintained below 18 mmHg, as demonstrated in the landmark Advanced Glaucoma Intervention Study [47].

In addition, a significant strength of this study was the completion of annual postoperative medication washouts, which isolate the

action of trabecular and suprachoroidal stents alone, without the effect of medication. At these post-washout visits (months 13, 25, 37, and 49), mean unmedicated IOPs remained near the 18-mmHg threshold, at 17.1–18.4 mmHg, representing a 30–35% reduction from preoperative mean unmedicated IOP, and a 16–22% reduction from preoperative mean medicated IOP. This IOP level suggests that, in the absence of a study protocol, some patients might be able to achieve target pressures and be managed without medications. This adds value, given that medications’ effectiveness may be limited by side effects, toxicities, cost, and patient adherence [40–46].

Based on IOP measurements during the study’s washout periods, it appears that the prostaglandin contributed approximately 4 mmHg of IOP lowering, equaling a reduction of approximately 15% from mean baseline unmedicated IOP. This decrease is less substantial than the ~ 30% IOP reductions typically expected with prostaglandin analogs [48]. This discrepancy likely reflects the refractory nature

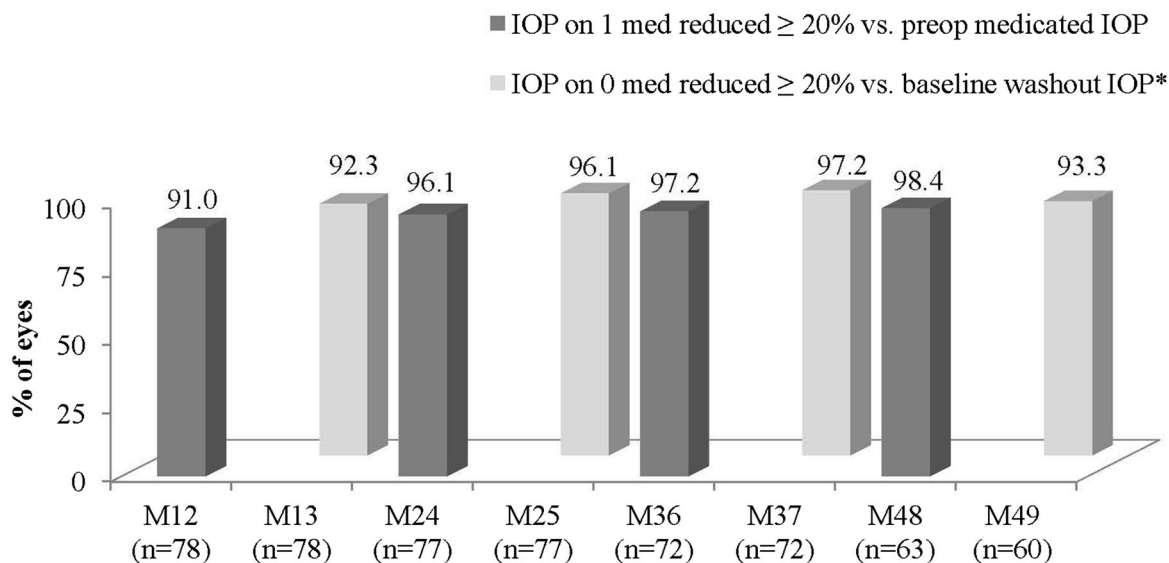


Fig. 4 Proportional analysis of postoperative IOP reduction $\geq 20\%$. *Unmedicated IOP (at months 13, 25, 37, 49) was assessed after 1-month washout. ^aExcludes data after cataract surgery ($n = 10$). Subjects with

additional glaucoma surgery ($n = 0$) or addition of a second ocular hypotensive medication ($n = 6$) were considered non-responders. IOP Intraocular pressure, Med medication, Preop preoperative, M month

of disease in these eyes with prior filtering surgery and medication use. The fact that the iStents and iStent Supra yielded sizable IOP reductions in this population is thus even more noteworthy.

The safety parameters observed in this study were favorable, including stable BCVA, visual fields, C:D ratio, and corneal pachymetry over the course of follow-up. There was one intraoperative report of inability to implant the suprachoroidal stent, but otherwise no intraoperative adverse events occurred. The most common postoperative adverse event was BCVA decrease due to cataract progression, which occurred in approximately 16% of eyes (11 of 70 by 4 years). However, this rate of cataract progression is lower than that of trabeculectomy, which is estimated to cause cataract in over 50% of subjects within 5 years [49]; furthermore, the study's cataract cases were successfully addressed with cataract surgery. There were no reports of suprachoroidal hemorrhage, persistent hypotony, infection, dysesthesia, hyphema, or iridodialysis. Over the course of follow-up, six eyes were prescribed a second medication, but all other eyes remained on travoprost alone. No

eyes underwent secondary glaucoma surgery throughout follow-up. This is especially significant given that many of these patients likely would otherwise have undergone such a surgery. These filtering surgeries have a well-documented ongoing annual risk of complications [21–30], which places a considerable cumulative burden on patients with this lifelong disease. Thus, even if some of these patients ultimately undergo additional intervention in the future, the delay-to-surgery of 4 or more years is valuable in itself by reducing this cumulative risk.

We acknowledge certain limitations in this nonrandomized, open-label study. All subjects were Caucasian, all visits occurred at a single site, and mean diurnal IOP was not measured at all visits. The relatively low values for IOP variance observed in this study appear consistent with variance in several prior reports of iStent technology [7, 50, 51]. There was no control arm; however, like in many other studies of standalone interventions, we considered it reasonable for subjects' preoperative data to serve as their own control. In addition, given that this refractory population already had failed filtering surgery and medication, no standard next-

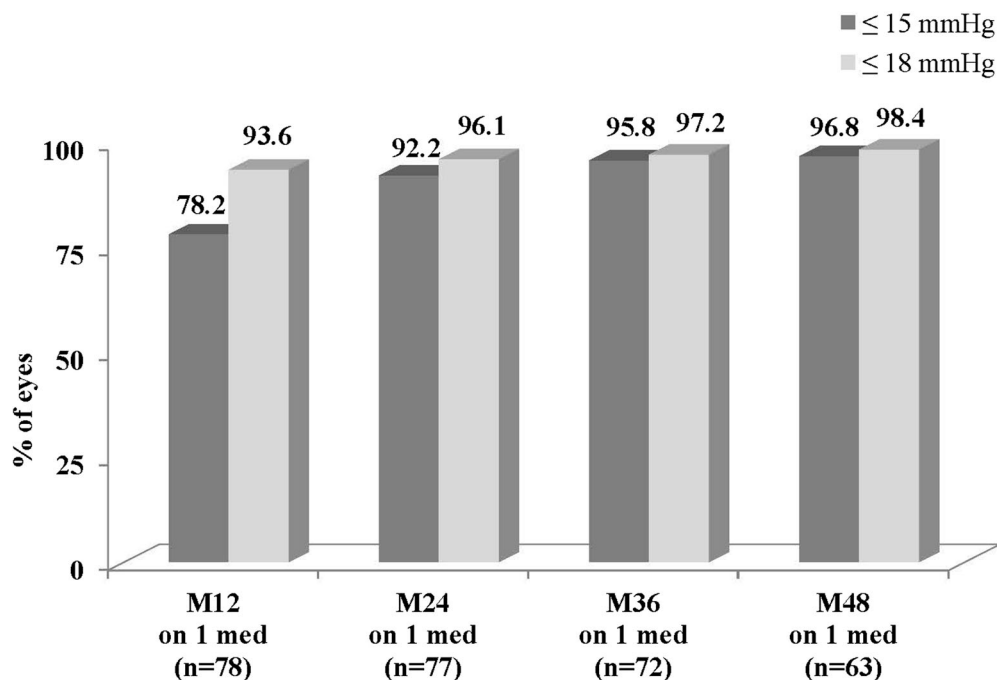


Fig. 5 Proportional analysis of postoperative IOP ≤ 15 and ≤ 18 mmHg. ^aExcludes data after cataract surgery (*n* = 10). Subjects with additional glaucoma surgery

(*n* = 0) or addition of a second ocular hypotensive medication (*n* = 6) were considered non-responders. *IOP* Intraocular pressure, *Med* medication, *M* month

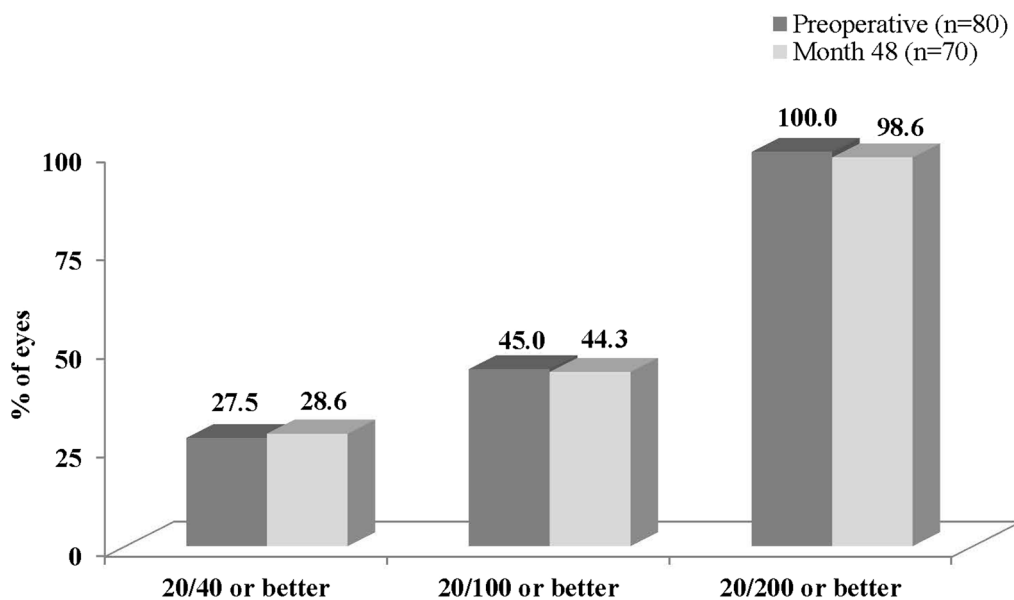


Fig. 6 Preoperative versus month 48 best-corrected visual acuity (BCVA)

step treatment was readily apparent. And third, since these refractory eyes were vulnerable to optic nerve damage and visual field

deterioration, a control group of minimal intervention would not have been clinically or ethically appropriate.

Given that all subjects underwent a combined treatment (two iStent trabecular stents, one iStent Supra suprachoroidal stent, and postoperative prostaglandin), it is not possible to quantify the isolated effect of each specific component on IOP. However, this study's simultaneous use of surgical and medical treatment has precedence in the literature, such as in the landmark Early Manifest Glaucoma Trial [52]. Additionally, the annual medication washouts provide an estimate of the devices' effect alone, which is a $\geq 30\%$ reduction in IOP. In future investigations, several alternative study designs could be considered in order to isolate the effects of each treatment modality. One such study design could have been a step-wise addition of one treatment at a time; however, this would have subjected subjects to additional surgery, and also might delay arrival at a sufficiently safe IOP for these refractory eyes. A second alternative design could be a multi-armed trial comparing different treatment combinations (for example: trabecular stents + suprachoroidal stent; trabecular stents + prostaglandin; suprachoroidal stent + prostaglandin; trabecular stents alone; or suprachoroidal stent alone); however, this also could produce an unsafe delay in reaching appropriate IOP, and would have required a much larger cohort to allow for meaningful comparisons. A third alternative design could be initial treatment with two iStents and travoprost, with subsequent "crossover" or "escape" to iStent Supra in cases of insufficient IOP reduction.

In this report, we have presented 4 years of follow-up data for this ongoing study, but full results with extended follow-up out to 61 months will provide even more robust insights into long-term outcomes for refractory disease under this treatment methodology. In addition, other directions for future investigation could include structural and functional testing to quantify glaucoma severity (possibly using novel imaging techniques), or evaluation of this treatment methodology in eyes with pseudoexfoliative glaucoma. And finally, the present study had a single treatment arm consisting of three interventions; however, in order to determine definitively whether combined MIGS

devices are a suitable alternative to additional incisional surgery, a randomized controlled study would be needed to directly compare traditional filtering surgery with combined trabecular/suprachoroidal stents and prostaglandin in these refractory eyes.

CONCLUSIONS

In conclusion, this study provides insights into a novel, minimally invasive technique and treatment regimen for the control of refractory glaucoma: specifically, the combined use of two trabecular micro-bypass stents, a suprachoroidal stent, and postoperative prostaglandin. Following this intervention, outcomes through 4 years demonstrate meaningful IOP and medication reductions, favorable safety, and avoidance of additional filtering surgery in the vast majority of refractory cases. These long-term outcomes indicate that the combination of multiple minimally invasive devices with medication may have a role in treating unresponsive or under-controlled refractory primary OAG, even while preserving ocular tissue for additional surgeries should they be warranted.

ACKNOWLEDGEMENTS

Funding. Sponsorship of this study and the open access fee were funded by Glaukos Corporation, San Clemente, CA, USA. Article processing charges were funded by Glaukos. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Disclosures. Jonathan S. Myers received support for study-related research activities from

Glaukos, and has received research grants and speaker fees from Alcon and Allergan. Jose I. Belda received support for study-related research activities from Glaukos, and has received speaker honoraria from Pfizer. Imran Masood is a consultant to Glaukos. Anselm Junemann is a consultant to Glaukos. Gerd Auffarth is a consultant to Glaukos. Jose M. Martinez-de-la-Casa received speaker honoraria and support for study-related research activities from Glaukos. Iqbal Ike K. Ahmed is a consultant to Glaukos. Dana M. Hornbeak is an employee of Glaukos. Jane Ellen Giamporcaro is an employee of Glaukos. Lilit Voskanyan received financial support from Glaukos for her work as an investigator in this study. L. Jay Katz received grant support from Allergan, Aerie Pharm., Mati Therapeutics, Diopsys, Heidelberg Eng., Alcon, and Zeiss; speaker honoraria from Alcon, Allergan, Bausch & Lomb, Aerie Pharm., and Glaukos; and a medical monitor consulting fee from Glaukos; he is a consultant to Allergan, Alcon, Glaukos, Aerie Pharm., Inotek, Mati Ther., Diopsys, and DSM Biomed; and he is a shareholder in Aerie Pharm., Glaukos, Mati Ther.

Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Armenian Ministry of Health) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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