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ORIGINAL RESEARCH

Treatment Success Across Different Levels of Preoperative Disease Burden: Stratified Two-Year Outcomes from the Pivotal Trial of iStent *inject*® Trabecular Micro-Bypass in Primary Open-Angle Glaucoma and Cataract

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Purpose: To examine effectiveness outcomes stratified by preoperative disease burden in the pivotal trial of iStent *inject*® with cataract surgery (INJ) vs cataract surgery alone (CS).

Materials and Methods: Prospective, 3:1 randomized, single-masked, concurrently-controlled, multicenter trial enrolling 505 subjects with cataract and mild-to-moderate primary open-angle glaucoma who underwent iStent *inject* implantation with phacoemulsification or phacoemulsification alone, and were followed for 2 years including annual medication washouts. Post hoc stratification was completed for baseline mean diurnal intraocular pressure (BL DIOP; Low-DIOP <25mmHg, Mid-DIOP ≥25 to <30 mmHg, High-DIOP ≥30mmHg) and preoperative medication burden (Low-Med 1 medication, Mid-Med 2 medications, High-Med ≥3 medications).

Results: The 24-month primary and secondary effectiveness endpoints were met, with significant treatment-over-control differences in percent of eyes achieving ≥20% unmedicated DIOP reduction and in unmedicated DIOP reduction, respectively. In subgroup analyses, the proportions of INJ eyes achieving the primary endpoint remained steady across all BL DIOP (75.4%, 77.1%, 74.4% in Low/Mid/High-DIOP strata, respectively) and preoperative medication levels (76.8%, 70.8%, 79.7% in Low/Mid/High-Med strata, respectively); meanwhile, the proportions of CS eyes diminished with higher BL DIOP (64.5%, 63.6%, 33.3%, respectively) and more medications (69.0%, 63.3%, 29.4%, respectively). Regarding secondary effectiveness, postoperative DIOP reduction increased with higher BL DIOP in INJ eyes (6.2mmHg, 7.8mmHg, 9.8mmHg, respectively) but plateaued in CS eyes (5.2mmHg, 5.8mmHg, 5.4mmHg, respectively). INJ eyes also had consistent DIOP reduction regardless of preoperative medication burden (6.8mmHg, 6.7mmHg, 7.8mmHg, respectively), while DIOP reduction diminished with more medications in CS eyes (6.1mmHg, 5.0mmHg, 3.3mmHg, respectively). Safety was favorable, comparable to phacoemulsification alone.

Conclusion: Significant IOP reductions occurred across all levels of BL DIOP and preoperative medication burden in iStent *inject* eyes. DIOP reductions increased with higher BL DIOP and remained stable across all levels of preoperative medication burden, suggesting the device's potential utility in more medically challenging cases.

Keywords: microinvasive glaucoma surgery/MIGS, glaucoma, iStent *inject*, trabecular micro-bypass, IOP, stratification, severity

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Introduction

Already the leading cause of irreversible blindness globally, glaucoma is expected to increase in prevalence from approximately 65 million people in 2013 to nearly 120 million in 2040.[1] The cornerstone of glaucoma treatment is IOP reduction, the only proven way to limit the progressive optic nerve damage associated with the disease. IOP reduction is unequivocally beneficial, with 1 mmHg of IOP reduction equating to 11–19% reduced risk of disease progression[2,3] and 10% reduced risk of glaucoma development in pre-glaucomatous eyes.[4] Currently-available glaucoma therapies range from medications and laser trabeculoplasty (more conservative) to filtering procedures like trabeculectomy and tube placement (more invasive). Between these extremes, a class of procedures known as micro- or minimally-invasive glaucoma surgery (MIGS) may offer a lower-risk alternative for reducing IOP and medication burden. Recent years have witnessed a marked rise in the use of MIGS procedures as an earlier intervention prior to (or ideally instead of) filtering procedures.[5] MIGS procedures seek to avoid the disadvantages of ocular hypotensive medication (eg, ocular surface disease, poor compliance, side effects, cost) and the risks of filtering surgeries (eg, dysesthesia, bleb leaks, hypotony, blebitis, and lifetime endophthalmitis risk).[6–10]

To-date, the most extensive body of MIGS evidence pertains to the first US Food and Drug Administration (FDA)-approved MIGS device, the Glaukos iStent® Trabecular Micro-Bypass. With up to 7 years of postoperative follow-up, iStent studies have often focused on patients with mild to moderate POAG undergoing cataract surgery, but an increasing number of studies have assessed iStent for different glaucoma types (eg, pseudoexfoliative, angle-closure, pigmentary), more advanced severity, standalone cases, and in combination with other procedures or stents.[11–23] The more recent iStent *inject*® Trabecular Micro-Bypass (CE Mark 2010, FDA approval 2018) contains two stents that create two patent bypasses through the diseased trabecular meshwork. This device has been studied both with and without concomitant cataract extraction, and in studies with up to 5 years of follow-up.[24–39]

Both iStent and iStent *inject* are implanted ab internally and enhance the physiologic trabecular outflow pathway of aqueous humor, thereby decreasing IOP. Targeting the natural outflow pathway helps avoid the risks of suprachoroidal, bleb-forming, subconjunctival, and/or ab externo procedures. Among trabecular MIGS, the microscale iStent *inject* is the only modality that avoids tissue destruction or removal, and that has the smallest known footprint designed to preserve angle structures. Importantly, stent implantation does not preclude additional medical or surgical therapies should they be needed later in this lifelong disease.

Several preoperative characteristics may shape the goal of glaucoma surgery; some of these also may predict postoperative outcomes. A common factor evaluated in the literature is baseline IOP. Studies in glaucomatous and healthy eyes have shown a consistent association between higher baseline IOP and greater postoperative IOP reduction.[40–43] In addition, several publications have shown this IOP association following iStent or iStent *inject* implantation.[15–18,26,27] Fewer studies have evaluated the relationship between preoperative medication burden and postoperative IOP reduction.[44,45] However, to our knowledge, no MIGS pivotal trials to-date have specifically explored outcomes with stratification by preoperative IOP and medications.

The present pivotal trial was a large randomized study evaluating iStent *inject* implantation with cataract surgery versus cataract surgery alone in patients with mild to moderate POAG and cataract. At two years postoperative, both the primary and secondary effectiveness endpoints were met (≥20% unmedicated DIOP reduction and mean unmedicated DIOP reduction, respectively).[24] The current manuscript examines these outcomes with stratification by baseline DIOP and preoperative number of medications, thereby assessing device viability across the spectrum of preoperative treatment burden and surgical goals.

Materials and Methods

Study Design, Endpoints, and Participants

This prospective, 3:1 randomized, single-masked, controlled, multicenter US pivotal trial evaluated the two-year safety and effectiveness of iStent *inject* in patients with mild to moderate POAG and cataract. The study design was 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 trial was approved by the Western Institutional Review Board (IRB) and followed the tenets of the Declaration of Helsinki, including written informed consent of all subjects. The study was registered with the

National Library of Medicine (clinicaltrials.gov, NCT00323284).

Key aspects from the complete inclusion/exclusion criteria, sample size calculations, randomization, effectiveness endpoints, medications, and postoperative follow-up[24] are summarized here. Subjects were randomized in a 3:1 ratio to the treatment group (cataract surgery + iStent *inject*, n=387, INJ) or control group (cataract surgery only, n=118, CS) after completion of uncomplicated cataract surgery; the randomization scheme was based on a computer-generated list. Throughout postoperative follow-up, subjects and the technicians performing postoperative measurements were masked to treatment assignment. The primary effectiveness endpoint was a ≥ 20% reduction from baseline in medication-free mean diurnal DIOP at Month 24. The secondary effectiveness endpoint was the unmedicated 24-month DIOP reduction from baseline. IOP measurements were taken by Goldmann applanation using a standard 2-person method common in glaucoma studies;[4] mean DIOP was calculated as the mean of three individual IOP measurements on the same day (at approximately 8:00 am, 12:00 pm, and 4:00 pm), and was performed at baseline and at Months 6, 12, and 24. Safety parameters included best spectacle-corrected visual acuity (BSCVA), slit-lamp and fundus examinations, gonioscopy, pachymetry, specular microscopy, visual field testing, adverse events (AEs), and complications. Patients underwent surgery from January 2012 to August 2015. Postoperatively, study visits occurred at 6 hours, Day 1, Week 1, and at Months 1, 3, 6, 11, 12, 18, 23, and 24. Prior to the preoperative baseline visit, and at the Month 11 and Month 23 postoperative visits, subjects using ocular hypotensive medication(s) were instructed to undergo medication washout in order to permit unmedicated DIOP assessment at baseline and at Months 12 and 24, respectively.

Key inclusion criteria included a diagnosis of mild to moderate POAG (with mean deviation not worse than −12dB), cataract requiring surgery, screening IOP ≤24 mmHg on 1–3 ocular hypotensive medications, and unmedicated baseline mean DIOP (BL DIOP) 21–36 mmHg. Patients were excluded if they had traumatic, uveitic, neovascular, angle-closure, or vascular-disorder-associated glaucoma; history of prior incisional glaucoma surgery, argon laser trabeculoplasty (ALT), iridectomy, or iridotomy, or completion of selective laser trabeculoplasty (SLT) within 90 days prior to screening; or ocular disease or visual field status that would preclude safe medication washout.

Study Device and Surgical Implantation Technique

As detailed previously,[24] the iStent *inject* device and implantation technique may be summarized as follows. Each single-use iStent *inject* injector is pre-loaded with two biocompatible titanium stents. Each stent has a central lumen and four side lumens to facilitate multi-directional outflow, and is designed to carry the entirety of aqueous humor production by the human body (average 2.5 µL/min).[46,47] The placement of two stents enables access to up to six clock-hours of collector channels, and has shown the ability to reactivate formerly dormant collector channels and enhance flow through active collector channels.[48]

Following phacoemulsification cataract extraction and intraocular lens insertion, the iStent *inject* injector is advanced under direct gonioscopy through the existing corneal incision to the nasal trabecular meshwork, where the first stent is implanted through the meshwork into Schlemm's canal. While remaining in the eye, the injector tip is repositioned to implant the second stent approximately 2 to 3 clock hours away from the first stent, and proper placement and seating are confirmed for both stents. Viscoelastic is then removed and sealing of the corneal incision is ensured. Following surgery, patients were prescribed topical antibiotics (for one week) and prednisolone acetate 1% (tapered over four weeks).

Statistical Analyses

For the baseline DIOP subgroup post hoc analyses, eyes were divided into three groups (Low-DIOP <25 mmHg, Mid-DIOP ≥25 to <30 mmHg, and High-DIOP ≥30mmHg). For the preoperative medication subgroup analyses, eyes also were divided into three groups (Low-Med, 1 medication; Mid-Med, 2 medications; and High-Med: ≥3 medications). Within each IOP or medication level, the mean reductions in IOP and medications were compared between the INJ and CS groups using a two-sample *t*-test. The proportion of eyes achieving a ≥20% DIOP reduction versus baseline was compared between INJ and CS eyes within each DIOP or medication stratum using a two-sided chi-square test. If 25% of the cells had expected counts less than 5, then Fisher's exact test was used.

Results

Effectiveness

The preoperative characteristics of the overall cohort from this randomized controlled pivotal trial were provided in the prior publication.[24] The distribution and demographic characteristics of the current stratified IOP and medication subgroups are provided in Tables 1 and 2, respectively.

The study met both the primary and secondary effectiveness endpoints: a significantly higher proportion of INJ eyes (75.8%) than CS eyes (61.9%) achieved a ≥ 20% reduction in medication-free DIOP from baseline at 24 months (p=0.005), and the mean reduction in medication-free DIOP from baseline to 24 months was significantly greater in treatment versus control eyes (p<0.001), respectively. Notably, the final IOP of INJ eyes without the use of any medications was 17.1 mmHg, comparable to or lower than other trabecular MIGS randomized controlled trials (RCTs).[24,49] Furthermore, iStent *inject* eyes reduced their mean medication burden by 75% (versus 47% in CS eyes), with 84% of stent eyes becoming medication-free at two years (vs 67% of control eyes), and a 50% lower final mean medication burden in stent eyes than control eyes (0.4 versus 0.8 medications, respectively; p<0.001).

Within the baseline DIOP strata, significant treatment-vs.-control differences in the proportion of eyes achieving a ≥ 20% DIOP reduction from baseline were observed regardless of BL DIOP (p<0.05 for all 3 IOP strata). In the three BL DIOP strata of the CS group (Low-DIOP n=76, Mid-DIOP n=33, High-DIOP n=9), the proportion of eyes reaching the endpoint was 64.5% in the Low-DIOP stratum, 63.6% in the Mid-DIOP stratum, and 33.3% in the High-DIOP stratum. In contrast, within the BL DIOP strata of the INJ group (Low-DIOP n=239, Mid-DIOP n=109, High-DIOP n=39), the proportions of INJ eyes achieving the endpoint remained steady across all levels of BL DIOP (75.4% in Low-DIOP stratum, 77.1% in Mid-DIOP stratum, and 74.4% in High-DIOP stratum) (Figure 1). In other words, iStent *inject* eyes with higher DIOP preoperatively appeared to be just as likely to achieve treatment success as iStent *inject* eyes with lower preoperative DIOP, a consistency that was not observed in the cataract-only CS group.

With regard to the secondary effectiveness outcome, the amount of postoperative DIOP reduction plateaued in CS eyes (5.2 mmHg in Low-DIOP stratum, 5.8 mmHg in Mid-DIOP stratum, and 5.4 mmHg in High-DIOP stratum) while it increased with higher baseline DIOP in INJ eyes (6.2 mmHg, 7.8 mmHg, and 9.8 mmHg in the three strata, respectively) (Figure 2).

Table 1 Preoperative Demographic Characteristics[a] of Subjects in the Low-DIOP, Mid-DIOP, and High-DIOP Strata

Parameter		Cataract Surgery with iStent *inject* (n=387)	Cataract Surgery Only (n=118)
Baseline DIOP <25 mmHg (Low-DIOP)			
n		239	76
Age (Years)	Mean ± SD	69.2 ± 8.7	71.2 ± 7.3
	Range	45–98	55–85
Gender	Male	92/239 (38.5%)	32/76 (42.1%)
	Female	147/239 (61.5%)	44/76 (57.9%)
Race/Ethnicity	White	167/239 (69.9%)	55/76 (72.4%)
	Hispanic/Latino	17/239 (7.1%)	7/76 (9.2%)
	Black	52/239 (21.8%)	12/76 (15.8%)
	Asian	3/239 (1.3%)	1/76 (1.3%)
	Other	0/239 (0.0%)	1/76 (1.3%)
Baseline DIOP ≥25 to < 30 mmHg (Mid-DIOP)			
n		109	33
Age (Years)	Mean ± SD	68.9 ± 7.5	68.6 ± 8.1
	Range	47–86	52–86
Gender	Male	47/109 (43.1%)	15/33 (45.5%)
	Female	62/109 (56.9%)	18/33 (54.5%)
Race/Ethnicity	White	88/109 (80.7%)	23/33 (69.7%)
	Hispanic/Latino	6/109 (5.5%)	3/33 (9.1%)
	Black	14/109 (12.8%)	6/33 (18.2%)
	Asian	0/109 (0.0%)	0/33 (0.0%)
	Other	1/109 (0.9%)	1/33 (3.0%)
Baseline DIOP ≥30 mmHg (High-DIOP)			
n		39	9
Age (Years)	Mean ± SD	67.8 ± 7.4	66.8 ± 8.6
	Range	48–79	46–72
Gender	Male	23/39 (59.0%)	7/9 (77.8%)
	Female	16/39 (41.0%)	2/9 (22.2%)
Race/Ethnicity	White	27/39 (69.2%)	8/9 (88.9%)
	Hispanic/Latino	1/39 (2.6%)	0/9 (0.0%)
	Black	11/39 (28.2%)	1/9 (11.1%)
	Asian	0/39 (0.0%)	0/9 (0.0%)
	Other	0/39 (0.0%)	0/9 (0.0%)

Note: [a] In the intent-to-treat (ITT) population, consisting of all randomized subjects.
Abbreviations: BL DIOP, baseline mean diurnal intraocular pressure; SD, standard deviation.

Table 2 Preoperative Demographic Characteristics[a] of Subjects in the Low-Med, Mid-Med, and High-Med Strata

Parameter		Cataract Surgery with iStent *inject* (n=387)	Cataract Surgery Only (n=118)
1 Ocular Hypotensive Medication at Screening (Low-Med)			
n		224	71
Age (Years)	Mean ± SD Range	68.6 ± 8.0 45–89	69.9 ± 8.3 46–85
Gender	Male Female	91/224 (40.6%) 133/224 (59.4%)	32/71 (45.1%) 39/71 (54.9%)
Race/Ethnicity	White Hispanic/Latino Black Asian Other	162/224 (72.3%) 18/224 (8.0%) 43/224 (19.2%) 1/224 (0.4%) 0/224 (0.0%)	52/71 (73.2%) 6/71 (8.5%) 11/71 (15.5%) 1/71 (1.4%) 1/71 (1.4%)
2 Ocular Hypotensive Medications at Screening (Mid-Med)			
n		98	30
Age (Years)	Mean ± SD Range	69.2 ± 7.8 49–88	70.7 ± 6.7 57–84
Gender	Male Female	41/98 (41.8%) 57/98 (58.2%)	15/30 (50.0%) 15/30 (50.0%)
Race/Ethnicity	White Hispanic/Latino Black Asian Other	78/98 (79.6%) 2/98 (2.0%) 16/98 (16.3%) 1/98 (1.0%) 1/98 (1.0%)	22/30 (73.3%) 2/30 (6.7%) 5/30 (16.7%) 0/30 (0.0%) 1/30 (3.3%)
≥3 Ocular Hypotensive Medications at Screening (High-Med)			
n		65	17
Age (Years)	Mean ± SD Range	69.6 ± 9.8 47–98	69.8 ± 7.2 56–86
Gender	Male Female	30/65 (46.2%) 35/65 (53.8%)	7/17 (41.2%) 10/17 (58.8%)
Race/Ethnicity	White Hispanic/Latino Black Asian Other	42/65 (64.6%) 4/65 (6.2%) 18/65 (27.7%) 1/65 (1.5%) 0/65 (0.0%)	12/17 (70.6%) 2/17 (11.8%) 3/17 (17.6%) 0/17 (0.0%) 0/17 (0.0%)

Note: [a]In the intent-to-treat (ITT) population, consisting of all randomized subjects.
Abbreviation: Med, medication; SD, standard deviation.

Outcomes also were analyzed in three subgroups based on the number of preoperative medications, which served as a proxy for disease treatment burden. In the medication strata of the CS group (Low-Med n=71, Mid-Med n=30, High-Med n=17), the proportion of eyes achieving the primary endpoint was 69.0% in the Low-Med stratum, 63.3% in the Mid-Med stratum, and 29.4% in the High-Med stratum. Meanwhile, within the medication strata of the INJ group (Low-Med n=224, Mid-Med n=98, High-Med n=65), the proportion of treatment eyes achieving the endpoint remained steady regardless of preoperative medication burden (76.8%, 70.8%, and 79.7% in the three strata, respectively) (Figure 3). In other words, iStent *inject* eyes with higher preoperative medication burden appeared to be just as likely to achieve treatment success as iStent *inject* eyes with fewer preoperative medications, a consistency that was not observed in the control group.

With regard to the secondary effectiveness outcome, the amount of postoperative DIOP reduction diminished with higher preoperative medication burden in CS eyes (6.1 mmHg in Low-Med stratum, 5.0 mmHg in Mid-Med stratum, and 3.3 mmHg in High-Med Stratum), whereas it remained stable regardless of preoperative medication burden in INJ eyes (6.8 mmHg, 6.7 mmHg, and 7.8 mmHg in the three strata, respectively) (Figure 4).

Safety

As reported in the pivotal publication,[24] safety was excellent in the iStent *inject* treatment group, comparable to phacoemulsification alone. This included results for BSCVA, visual field MD, C:D ratio, and endothelial cell stability. There were no unanticipated adverse events and no cases of significant inflammatory responses, myopic shift, choroidal hemorrhage or effusion, hypotony, stent dislocation or migration, significant hyphema, corneal decompensation, shallow anterior chamber, cyclodialysis, or endophthalmitis. The rate of peripheral anterior synechiae was low (1.8%). Over two years of follow-up, the rate of incisional glaucoma surgery was 1% in both INJ and CS eyes.

Discussion

Given the range of available therapies, choosing an appropriate intervention must account for patients' preoperative characteristics and individual surgical goals. Such factors may be ocular (eg, baseline IOP, medications, glaucoma severity) as well as non-ocular (eg, medication compliance, ocular surface health, and quality of life[39]). The ocular factors (specifically IOP and medications) undergoing stratified analysis in this study show consistency with the majority of the literature.[40–43] For example, two prominent publications

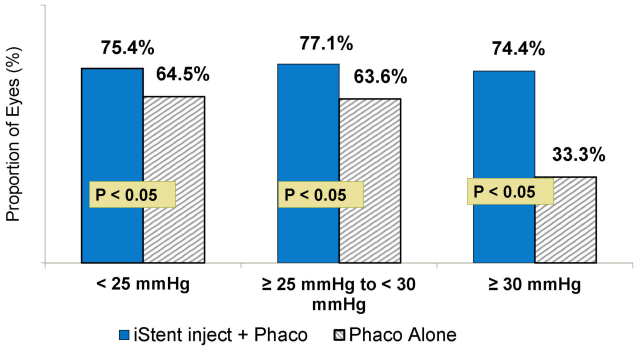

Figure 1 Proportion of Subjects with 24-Month Medication-Free Mean Diurnal Intraocular Pressure (DIOP) Reduction ≥20% from Baseline, Stratified By Baseline DIOP.

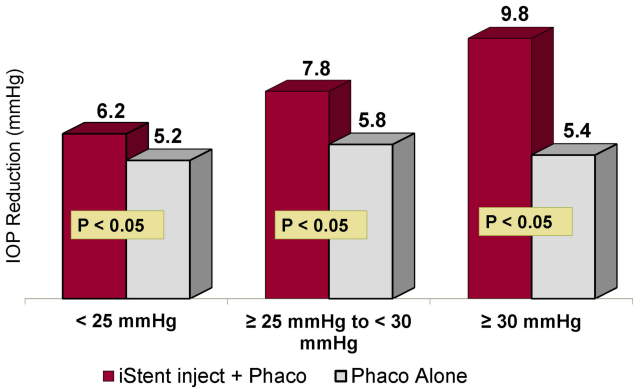

Figure 2 Average 24-Month Medication-Free Mean Diurnal Intraocular Pressure (DIOP) Change from Baseline, Stratified By Baseline DIOP.

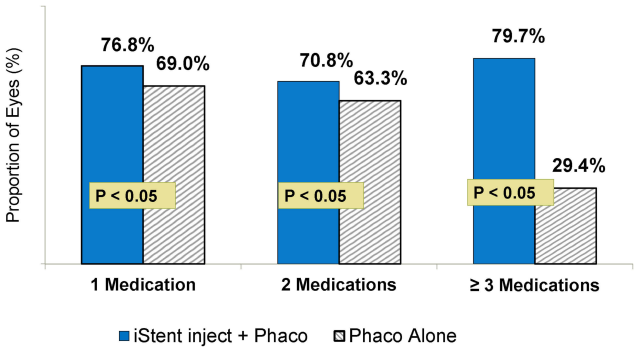

Figure 3 Proportion of Subjects with 24-Month Medication-Free Mean Diurnal Intraocular Pressure (DIOP) Reduction ≥20% from Baseline, Stratified By Number of Ocular Hypotensive Medications at Screening.

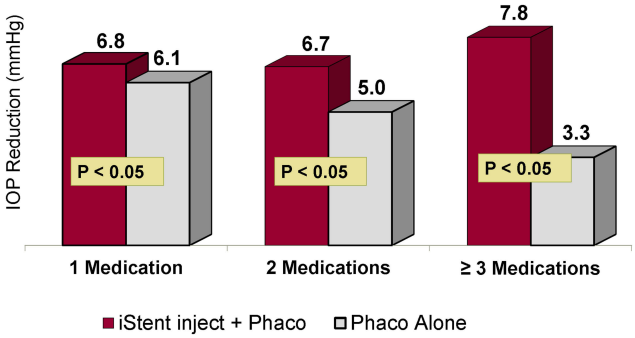

Figure 4 Average 24-Month Medication-Free Mean Diurnal Intraocular Pressure (DIOP) Change from Baseline, Stratified By Number of Ocular Hypotensive Medications at Screening.

of phacoemulsification cataract surgery in healthy[41] and glaucomatous[42] eyes showed that the amount of postoperative IOP reduction was proportional to preoperative IOP, with approximately three-fold higher percent reduction in the highest-IOP subgroups than in the 15–17 mmHg subgroup. This trend also is widely recognized in glaucomatous eyes undergoing combined phacoemulsification and glaucoma procedures,[50,51] and specifically in eyes undergoing iStent or iStent *inject* implantation either with or without phacoemulsification.[15–18,26,27]

In contrast to the predominant consensus in the literature, four recent non-controlled, non-randomized studies have suggested that success rates are higher in eyes with lower, rather than higher, disease burden: for example, in eyes with lower baseline IOP[44,52] or lower IOP during the first postoperative month;[45] lower number of preoperative medications;[44,45,52] or lower glaucoma severity according to VF MD.[45,53] However, attention must be paid to how these studies defined postoperative success; specifically, none of the studies' success criteria were adjusted for patients' preoperative IOP/medication burden or individual goals for surgery. As such, the criteria were not necessarily consistent with expectations of doctors and patients in real-world clinical practice. For example, Guedes et al and Rothschild et al required eyes to be on zero medications while achieving a fixed IOP value of <18 mmHg or ≤18 mmHg, respectively; Chansangpetch et al required eyes to be at a set postoperative IOP value of 18/15/12 mmHg for mild/moderate/severe cases, respectively; and Konopinska required eyes to be on zero medications postoperatively. Given these criteria, it is no surprise that eyes with lower preoperative IOP or medications are more likely to achieve the success threshold; this can be expected, as not all eyes had the same starting point.

Regardless of how success is defined in any given study, from a clinical perspective, it is unlikely that patients with high preoperative IOP and/or medication burden would realistically expect to achieve normotensive IOP with zero medications after MIGS surgery. In these patients (who comprise a substantial portion of the

glaucoma population), an operative "success" may be defined differently based upon patients' individual needs: for example, reducing IOP (with stable medications), reducing medications (with stable IOP), reducing exposure to topical drops and harmful preservatives, conserving conjunctival and trabecular tissue, and/or avoiding filtration surgery. Thus, to apply a single uniform postoperative goal to all eyes regardless of preoperative glaucoma status is inappropriate for many patients, as it would not take into account preoperative characteristics (in particular IOP and medications) nor surgical goals. A more appropriate threshold of success might be percent or amount of IOP reduction (rather than a fixed absolute IOP value), as well as reduction in medications, as these would accommodate heterogeneous preoperative characteristics. Not surprisingly, it is such baseline-sensitive endpoints that the FDA requires, given their clinical relevance and appropriateness.

Some authors have postulated that medication burden and/or IOP level can be considered a proxy for the degree of glaucomatous pathology in the trabecular meshwork, suggesting that eyes with more preoperative medications or with higher baseline IOP are more likely to have dysfunctional or dormant trabecular outflow networks.[45] However, this hypothesis is countered by the stratified results in the present large, randomized, controlled trial, in which greater IOP reductions were observed in eyes with higher baseline IOP and medications. It is also countered by aqueous angiography findings in eyes following iStent *inject* implantation,[48] which show clear reactivation of formerly dormant outflow areas, thereby suggesting that both trabecular and non-trabecular outflow networks may be restored via a trabecular (physiologic) intervention, without employing higher-risk suprachoroidal, subconjunctival, or more extensive tissue-disrupting MIGS procedures.

At every level of disease severity, a core principle of surgical glaucoma treatment is to implement the safest, least invasive technology that will achieve the treatment objectives. Consistent with these objectives, the safety profile of iStent *inject* was excellent, as summarized in the prior pivotal publication. Secondary filtration surgery occurred in very few eyes. Importantly, there were no complications as seen with filtering surgeries, such as endophthalmitis, hypotony, bleb infections, bleb leaks, and subconjunctival fibrosis.[6–10]

The main study limitations are that surgeons could not be masked to treatment assignment (given the surgical nature of the treatment intervention), and that data included the surgeons' learning curve with the technology. The former issue was counterbalanced by the use of a masked 2-person IOP measurement method, and the masking of subjects and technicians performing postoperative measurements; the latter aspect suggests that real-world outcomes of present-day surgeons actually may prove to be better than those observed in the study. Another limitation is the modest sample sizes within certain IOP or medication subgroups, as the study was not specifically designed to analyze these subgroups.

Conclusions

This pivotal study of the second-generation iStent *inject* trabecular micro-bypass device demonstrated significant, sustained, and safe clinical benefit of device implantation with cataract surgery in subjects with mild to moderate POAG. The IOP findings are meaningful given the well-established importance of IOP reduction; the medication reduction is also highly relevant, given the association of medications with ocular surface disease, increased future surgical failure, poor compliance, costs, diminished quality of life, and side effects.[39,54–57]

The additional stratification completed in the current analysis provides a greater understanding of iStent *inject* utility in patients with a range of IOP and medication levels along the disease spectrum. By grouping patients according to preoperative glaucoma treatment burden (specifically IOP and medications), a variety of possible surgical goals could be represented. Such goals could range from simply reducing medications to avoiding filtering surgery. In the present stratified analyses, it became apparent that the treatment-over-control advantage was greater, rather than smaller (as is sometimes assumed), in eyes with higher preoperative DIOP and more preoperative medications.

In addition, as previously described,[24] the safety outcomes observed in the pivotal trial were excellent, comparable to cataract surgery alone. This high safety, combined with the stratified effectiveness outcomes revealed in the present report, reinforce the viability of iStent *inject* with cataract surgery as an initial intervention prior to riskier, more invasive treatments. The stratified results suggest that treatment viability may extend to patients across the spectrum of preoperative treatment burden. By analyzing different stratified subgroups, from well-controlled cases aiming for medication reduction to uncontrolled cases aiming to reduce IOP and avoid filtrating surgery, the current analysis informs surgeons of the

postoperative IOP results that could reasonably be expected for patients at each level of disease burden.

Data Sharing Statement

Additional details from this clinical trial are available on the US FDA website and the clinicaltrials.org clinical trials registry, including the complete Summary of Safety and Effectiveness Data (SSED) document. Should further inquiries regarding de-identified individual participant data arise, a response and supporting documentation may be made available by the authors (Dr. Dana Hornbeak, dhornbeak@glaukos.com) on reasonable request.

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Disclosures

Dr Singh:

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Dr Sarkisian:

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