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Long-Term Endothelial Safety Profile With iStent *Inject* in Patients With Open-Angle Glaucoma

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• PURPOSE: To report 5-year postoperative safety data of iStent *inject*, including overall stability, endothelial cell density (ECD), and endothelial cell loss (ECL) in patients with mild-to-moderate primary open-angle glaucoma (POAG).

• DESIGN: 5-year follow-up safety study of the prospective, randomized, single-masked, concurrently controlled, multicenter iStent *inject* pivotal trial.

• METHODS: In this 5-year follow-up safety study of the 2-year iStent *inject* pivotal randomized controlled trial, patients receiving iStent *inject* placement and phacoemulsification or phacoemulsification alone were studied for the incidence of clinically relevant complications associated with iStent *inject* placement and stability. Corneal endothelial endpoints were mean change in ECD from screening and proportion of patients with >30% ECL from screening, from analysis of central specular endothelial images by a central image analysis reading center at several time points through 60 months postoperatively.

• RESULTS: Of the 505 original randomized patients, 227 elected to participate (iStent *inject* and phacoemulsification group, n = 178; phacoemulsification-alone control group, n = 49). No specific device-related adverse events or complications were reported through month 60. No significant differences were observed in mean ECD, mean percentage change in ECD, or proportion of eyes with >30% ECL between the iStent *inject* and control groups at any time point; mean percentage decrease in ECD at 60 months was 14.3% ± 13.4% in the iStent *inject* group and 14.8% ± 10.3% in the control group ($P = .8112$). The annualized rate of ECD change from 3 to 60 months was neither clinically nor statistically significant between groups.

• CONCLUSIONS: Implantation of iStent *inject* during phacoemulsification in patients with mild-to-moderate POAG did not produce any device-related complications or ECD safety concerns compared to phacoemulsification alone through 60 months. (Am J Ophthalmol 2023;252: 17–25.

THE LEADING WORLDWIDE CAUSE OF IRREVERSIBLE blindness is glaucoma. As of 2020, glaucoma caused blindness in more than 3 million people globally and was the cause of blindness in approximately 1 in 10 blind adults aged 50 years or older.[1] Furthermore, more than 4 million people aged 50 years or older have moderate to severe vision impairment from glaucoma.[1] Microinvasive glaucoma surgery (MIGS) with trabecular microbypass is capable of re-establishing physiological outflow, thereby reducing intraocular pressure (IOP) in the eye.[2] MIGS enables early surgical intervention in patients with mild to moderate open-angle glaucoma (OAG). In addition, MIGS procedures have fewer sight-threatening complications compared with the bleb-forming surgical treatments that create an artificial outflow pathway for aqueous humor[3]; such complications can include decreased visual acuity, bleb infections, and increased lifetime risk of bacterial endophthalmitis.

One of the major hallmarks of MIGS is the high safety profile associated with the procedure.[4] The iStent *inject* Trabecular Micro-Bypass System Model G2-M-IS (Glaukos Corporation) is approved by the United States Food and Drug Administration for use in conjunction with cataract surgery for the reduction of IOP in adult patients with mild to moderate primary open-angle glaucoma (POAG).[5] The 2-stent system of the iStent *inject* creates 2 patent bypasses through the trabecular meshwork, thus restoring the eye's natural outflow pathway. Prior studies of iStent *inject* have demonstrated durable and safe reductions in both IOP and medication burden, either with[6-9] or with-

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out[10-12] concomitant cataract surgery. The 2-year pivotal trial[13] evaluated the efficacy and safety of iStent *inject* implantation in cataract patients with mild to moderate POAG. This trial found that iStent *inject* implantation with phacoemulsification produced clinically meaningful reductions in IOP compared to phacoemulsification alone. In addition, the group of patients implanted with iStent *inject* and the control group had similar overall safety profiles throughout the 2-year postoperative follow-up period, which included measurements of best spectacle-corrected visual acuity (BSCVA), slitlamp and fundus examinations, gonioscopy, pachymetry, visual fields, complications, adverse events, secondary surgical interventions, and central endothelial cell density (ECD) determined from specular microscopic images.[13]

The monitoring of ECD and endothelial cell loss (ECL) over time have emerged as key safety outcomes in MIGS procedures.[14,15] In a typical adult eye, the ECD is 2000 to 3500 cells/mm^2, and corneal decompensation can occur when the rate of ECL is accelerated and the remaining endothelial cells cannot compensate with an increase in the density of pump sites to maintain epithelial and stromal thickness and clarity.[16,17] Natural ECL occurs with increasing age and can accelerate after intraocular surgery in patients with glaucoma.[18-21] The corneal endothelium does not proliferate in response to ECL.[22] Therefore, the preservation of ECD is of key importance for patients with chronic eye diseases or ocular comorbidities, such as open-angle glaucoma, that require surgical treatments. The objective of the current study is to report long-term corneal endothelial safety data of iStent *inject*, including ECL, up to 60 months postoperatively.

METHODS

• **STUDY DESIGN AND POPULATION:** The iStent *inject* pivotal trial[13] was a prospective, randomized, single-masked, concurrently controlled, multicenter clinical trial that enrolled eyes with mild to moderate POAG and preoperative IOP ≤24 mm Hg on 1 to 3 medications, unmedicated diurnal IOP 21 to 36 mm Hg, and cataract requiring surgery. At entry, patients were aged ≥45 years and had minimum central ECD at screening of 2000 cells/mm^2 for those aged 46 to 55 years, 1800 cells/mm^2 for those aged 56 to 65 years, and 1600 cells/mm^2 for those aged ≥65 years. Following uncomplicated cataract surgery, eyes were randomly assigned 3:1 intraoperatively to ab interno implantation of iStent *inject* (iStent *inject* group) or no stent implantation (phacoemulsification-only control group). The study followed the tenets of the Declaration of Helsinki (2008), was Health Insurance Portability and Accountability Act (HIPAA) compliant, and was approved prospectively by the Western Institutional Review Board (IRB). All subjects gave informed consent on the IRB-approved Informed Consent form for treatment and study participation. The study was registered with the National Library of Medicine (clinicaltrials.gov, NCT00323284).

All patients completing the 2-year iStent *inject* pivotal trial were invited to participate in this 5-year safety extension. Inclusion criteria for this 5-year follow-up study were as follows: (1) participation in the original 2-year trial; (2) willingness to attend scheduled follow-up examination for 5 years postoperatively; and (3) written informed consent on the IRB-approved informed consent form. Patients who did not participate in this study included those who met the following criteria: (1) declined participation, (2) were at a site that declined to participate; (3) died before the end of the 5-year follow-up period; (4) were unable to participate for non-ophthalmic medical reasons or non-medical reasons; (5) were at a site that had closed at the time of pre-market approval submission. To evaluate selection bias and to ensure that the 5-year extension population was representative of the original study population, demographic information, ocular parameters, and ECD outcomes were compared between patients who participated vs those who did not participate in the extension study. Selection bias was further assessed by evaluating the reasons for non-participation in the extension study between the iStent *inject* group and the phaco-only control group. Finally, to check for any possible pre-existing differences that could confound outcomes, complete preoperative demographic and ocular parameters were provided and compared for the stent-phaco group and phaco-only control group at the time of extension study enrollment.

• **STUDY ENDPOINTS AND SPECULAR MICROSCOPY:** The endpoints of the study included an overall safety endpoint of incidence of clinically relevant complications associated with iStent *inject* placement and stability through the 60-month follow-up, mean change in ECD from screening, and the proportion of patients with >30% ECL from screening. The annualized rate of ECD change from 3 to 60 months postoperatively was estimated to assess the period after the initial postoperative trauma. To measure these corneal endothelial endpoints, images of the central corneal endothelium were obtained via specular microscopy (Konan Medical Inc) at screening and at 3, 6, 12, 24, 36, 48, and 60 months postoperatively. Three images were obtained per eye at each time point. These images were evaluated in a masked fashion at an independent image analysis reading center (Cornea Image Analysis Reading Center [CIARC], University Hospitals Eye Institute, Cleveland, OH). All images were graded by 2 certified readers using the Konan center method to determine ECD, the coefficient of variation (CV), and the percentage of hexagonal cells (% HEX).[23,24] For quality control, a ≥5% difference in ECD determined by the 2 readers, or ≥15% differences in CV and % HEX, were adjudicated by a third reader.

• **STUDY DEVICE:** The study device was iStent *inject*. The IOP-lowering performance and safety profile of this device have been described previously in the 2-year trial.[13] Briefly, the iStent *inject* facilitates aqueous outflow through the trabecular meshwork into the Schlemm canal to decrease IOP. The iStent *inject* injector is preloaded with 2 titanium stents (each 230 µm in diameter, 360 µm in height, 80 µm in central lumen diameter). Each stent is capable of handling the average total amount of aqueous humor produced (2.5 µL/min) by the human eye using four 50-µm side outlets for aqueous outflow.

• **STATISTICAL ANALYSIS:** Descriptive statistics for continuous variables were mean and SD, and those for categorical variables were frequency and percentage. Two-sample *t* tests were used, assuming equal variance, to assess the difference in the mean central ECD between treatment groups at each visit. Pearson χ^2 tests were used to determine the difference between treatment groups in the proportion of patients with >30% central ECL from screening at each visit. When any expected subgroup count was <5 and therefore too small for an acceptable χ^2 approximation, the Fisher exact test was used instead. Two-sided *P* values <.05 were considered significant.

A linear model accounting for repeated measures within subject, with explanatory variables of treatment, month, and treatment-by-month interaction, was used to estimate the annualized rate of ECD change between 3 and 60 months postoperatively. A *P* value of <.05 indicated statistical significance.

RESULTS

A total of 505 participants in the 2-year trial were eligible for enrollment; 227 were enrolled in the extension study (178 in the iStent *inject* group and 49 in the control group, roughly proportional to the 3:1 randomization in the original protocol) (Figure 1). This represented 46.1% (178/386) of the iStent *inject* group and 41.2% (49/119) of the control group (*P* = .344). No study outcome–related differences existed between the iStent *inject* and control groups in the reasons for non-enrollment in the 5-year extension study. All enrolled subjects were assessed within or beyond the 60-month postoperative visit window.

The demographics of subjects enrolled in the current study are summarized in Table 1. The mean (SD) length of follow-up from surgery to final visit was 6.2 (0.9) years in the iStent *inject* with phacoemulsification group, and 6.3 (0.9) years in the phacoemulsification-alone control group. The mean (SD) age of enrollment was 75.2 (8.0) years in the iStent *inject* group and 75.6 (7.2) years in the control group. No significant demographic or ocular differences existed between the iStent *inject* group and the control group at the time of extension-study enrollment (Table 1). To ensure that protocol-driven selection bias was minimized in the 5-year follow-up population, an analysis was performed comparing the subjects who continued into this study population vs subjects who did not continue after pivotal study completion at 2 years. Although the groups differed slightly in baseline VF and visual acuity, no study outcome–related demographic or ECD differences were detected at screening or at 24 months between the group of patients who enrolled in this extension study and the group of patients who did not enroll (Supplemental Tables 1-3) aside from minor differences in visual acuity and mean deviation perimetry scores.

The overall safety endpoint was the incidence of clinically relevant complications associated with iStent *inject* placement and stability as determined at 60 months. Specific device-related complications could include, but were not limited to, secondary surgical interventions to modify device position (eg, repositioning or explantation) or to address corneal endothelial touch by device. No clinically relevant complications were associated with iStent *inject* placement and stability at 60 months (rate of 0%), so no Kaplan–Meier statistical analyses were indicated.

Regarding corneal endothelial safety, the most substantial decline in ECD occurred within the first 3 months postoperatively in both groups. The mean change from screening in ECD at 3 months was 284 ± 326 cells/mm^2 (11.3%) in the iStent *inject* group, which was similar to that in the control group (281 ± 333 cells/mm^2; 11.9%). Mean ECD at 3 months was 2166 ± 408 cells/mm^2 in the iStent *inject* group vs 2160 ± 493 cells/mm^2 in the control group (*P* = .931). After 3 months, mean ECD remained relatively stable, with only minimal decline through 60 months. At month 60, the mean change in ECD from screening was 355 ± 329 cells/mm^2 (14.3%) in the iStent *inject* group, which was similar to that in the control group (355 ± 247 cells/mm^2; 14.8%) (*P* = .811). Mean ECD at 60 months was 2099 ± 430 cells/mm^2 in the iStent *inject* group vs 2103 ± 419 cells/mm^2 in the control group (*P* = .954). There were no significant differences in the mean ECD or the percentage change in ECD between the iStent *inject* and control groups at any time point within the 60-month postoperative follow-up period (Table 2, Figure 2).

From 3 to 60 months postoperatively, the annualized rate of ECD decrease for the iStent *inject* group was estimated to be 19.2 cells/mm^2 (*P* < .0001) and for the control group 21.6 cells/mm^2 (*P* = .001). The difference between groups was neither clinically nor significantly different (2.4 cells/mm^2, *P* = .745). There were no statistically or clinically significant differences in the percentage of eyes with ECL >30% at 60 months in the iStent *inject* group (16/170, or 9.4%) vs the control group (3/48, or 6.3%) (*P* = .772). In addition, there were no significant differences in the percentage of eyes with ECL >30% between the iStent *inject* and control groups at any time point within the 60-month follow-up period (Figure 3). None of

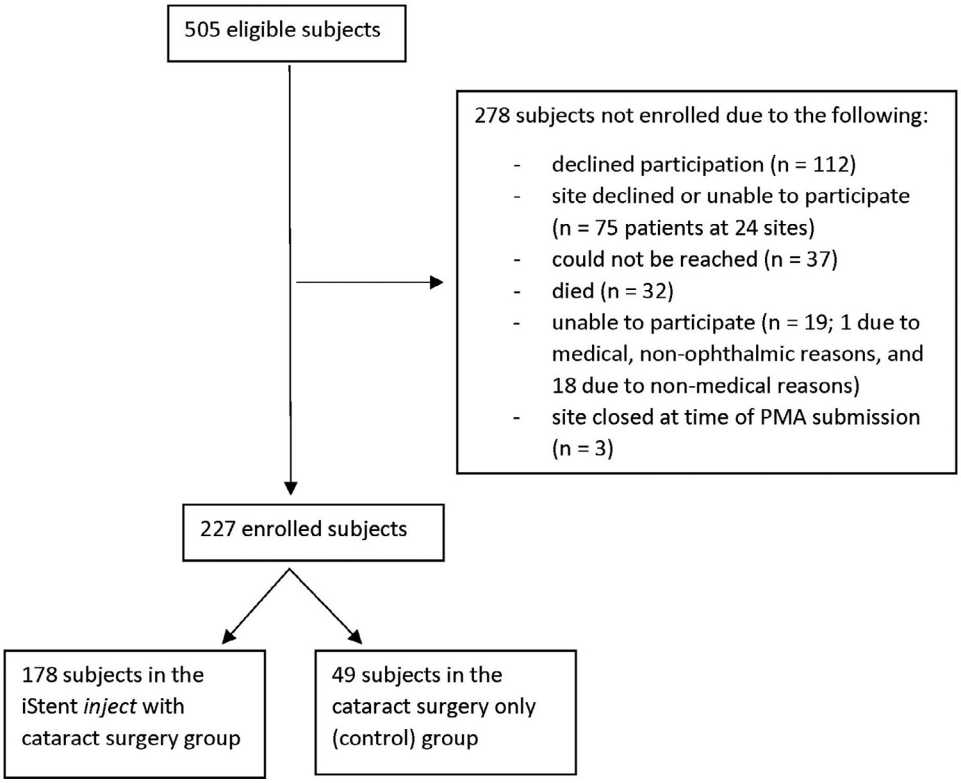

FIGURE 1. Study enrollment. A total of 227 patients were enrolled in the current study, of 505 eligible subjects from the 2-year pivotal trial of iStent *inject*.[13] Of the 227 enrolled patients, 178 received iStent *inject* implants with concomitant phacoemulsification, and 49 received phacoemulsification alone.

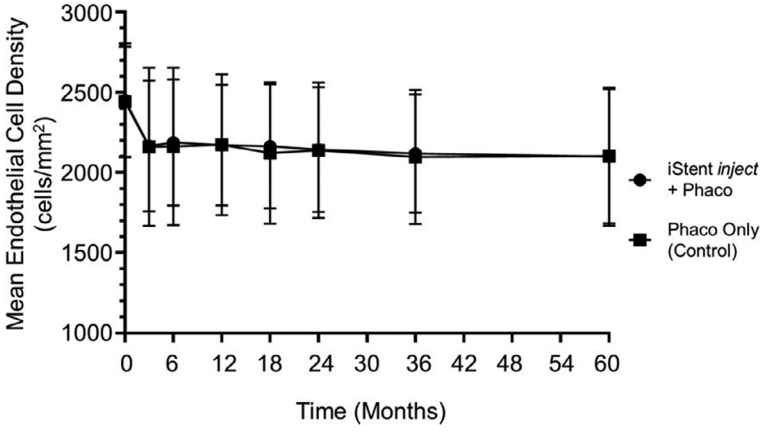

FIGURE 2. Five-year trend in endothelial cell density from screening. No significant differences in endothelial cell density were observed at any time point within the 60-month follow-up period between the iStent *inject* group and control group. At 60 months, the respective mean endothelial cell density was 2099 ± 430 cells/mm^2 and 2103 ± 419 cells/mm^2 in the iStent *inject* and the control groups (P = .954).

the eyes in this study developed corneal edema and/or required keratoplasty, none had ECD <750 cells/mm^2 at the 60-month visit, and there were no cases of corneal edema onset in eyes >30 days postoperative through the 60-month examination.

Data on endothelial cell morphology and central corneal thickness are summarized in Table 2. The mean percentage of hexagonal cells (HEX) was similar in the 2 groups over the 60-month follow-up. The mean coefficient of variation (CV) also was similar in the 2 groups over the same time

TABLE 1. Study Subject Demographics and Ocular Parameters

Characteristic	iStent *inject* With Phacoemulsification (iStent *inject*; n = 178)	Phacoemulsification Only (Control; n = 49)	*P* Value
Sex, n (%)			
Male	83 (46.6)	19 (38.8)	.418[a]
Female	95 (53.4)	30 (61.2)	
Race, n (%)			
American Indian	1 (0.6)	0 (0)	.580[a]
Asian	2 (1.1)	1 (2.0)	
Black	32 (18.0)	5 (10.2)	
Hispanic/Latino	10 (5.6)	3 (6.1)	
White	133 (74.7)	40 (81.6)	
Study Eye, n (%)			
OD	104 (58.4)	32 (65.3)	.415[a]
OS	74 (41.6)	17 (34.7)	
Age at surgery, y			
Mean (SD)	69.0 (7.8)	69.3 (7.0)	.818[b]
Range	49-86	52-84	
Age at Extension Study Enrollment, y			
Mean (SD)	75.2 (8.0)	75.6 (7.2)	.760[b]
Range	54-93	58-90	
Time From Surgery to Final Visit, days			
Mean (SD)	2271.6 (335.6)	2291.0 (323.7)	.714[b]
Range	1753-3098	1781-3005	
BSCVA (logMAR)			
Mean (SD)	0.19 (0.14)	0.19 (0.13)	.766[b]
Minimum, maximum	–0.1, 0.74	–0.08, 0.66	
Visual Field Mean Deviation (dB)			
Mean (SD)	–2.83 (3.26)	–2.69 (2.71)	.759[b]
Minimum, Maximum	–11.27, 3.12	–11.67, 1.79	
Visual Field Pattern SD (dB)			
Mean (SD)	3.24 (2.44)	2.86 (2.01)	.260[b]
Minimum, Maximum	1.13, 13.84	1.3, 10.76	
Central Corneal Thickness (μm)			
Mean (SD)	548.6 (36.2)	548.4 (37.3)	.974[b]
Minimum, Maximum	457, 620	451, 620	
Vertical C:D Ratio			
Mean (SD)	0.61 (0.15)	0.58 (0.20)	.237[b]
Minimum, Maximum	0.2, 0.8	0.2, 0.8	

dB = decibels; BSCVA = best spectacle-corrected visual acuity; C:D = Cup:Disc; y = years.
[a]Fisher exact test.
[b]Two-sample *t* test.

period. Neither the HEX nor the CV showed a substantial difference from screening values.

DISCUSSION

In the present study, we evaluated the 5-year safety profile of the iStent *inject* with concomitant phacoemulsification compared to phacoemulsification alone. Notably, patients who participated in this 5-year follow-up study did not experience any clinically relevant complications associated with iStent *inject* placement and stability. No secondary surgical interventions were required to modify device position, to address corneal endothelial touch by device, or to treat corneal edema leading to decreased BSCVA. Related to corneal endothelial health and structure, we found that there were no significant differences in ECD and ECL endpoints between the iStent *inject* with phacoemulsification group and the phacoemulsification-alone control group at any time points throughout the 5-year follow-up period. The largest postoperative reduction in ECD occurred between screening and 3 months in both the iStent *inject* group and the control group, most likely representing initial surgical trauma, and there was only minimal ECL thereafter. Based on the annualized rate of ECD change, we estimated no statistically significant dif-

TABLE 2. Five-Year Postoperative Changes in Endothelial Cell Density With iStent *inject* With Phacoemulsification Compared to Phacoemulsification Alone

Time (mo)	0 (Screening)	Month 3	Month 6	Month 12	Month 18	Month 24	Month 36	Month 60
n								
iStent *inject*	178	170	172	170	166	171	76	170
Control	49	49	47	49	45	47	18	48
ECD (cells/mm^2, Mean ± SD)								
iStent *inject*	2450 ± 355	2166 ± 408	2187 ± 393	2171 ± 376	2164 ± 387	2143 ± 389	2119 ± 368	2099 ± 430
Control	2441 ± 344	2160 ± 493	2163 ± 491	2173 ± 439	2122 ± 440	2139 ± 422	2097 ± 417	2103 ± 419
P value	.875	.931	.726	.975	.532	.951	.825	.954
Decrease in ECD From Screening (cells/mm^2, Mean ± SD)								
iStent *inject*	N/A	284 ± 326	268 ± 309	278 ± 297	289 ± 292	302 ± 292	267 ± 268	355 ± 329
Control	N/A	281 ± 333	268 ± 327	268 ± 281	303 ± 288	305 ± 252	366 ± 237	355 ± 247
Percentage Decrease in ECD From Screening (Mean ± SD)								
iStent *inject*	N/A	11.3 ± 12.7	10.6 ± 12.2	11.0 ± 11.7	11.5 ± 11.5	12.1 ± 11.5	11.1 ± 10.7	14.3 ± 13.4
Control	N/A	11.9 ± 14.8	11.4 ± 14.3	11.2 ± 12.2	12.8 ± 12.4	12.8 ± 11.0	15.2 ± 9.6	14.8 ± 10.3
Eyes With ECL >30% From Screening, n (%)								
iStent *inject*	N/A	19 (11.2)	18 (10.5)	11 (6.5)	13 (7.8)	16 (9.4)	5 (6.6)	16 (9.4)
Control	N/A	7 (14.3)	6 (12.8)	5 (10.2)	4 (8.9)	2 (4.3)	1 (5.6)	3 (6.3)
CV[a] (Mean ± SD)								
iStent *inject*	33.3 ± 4.22	32.9 ± 3.66	32.3 ± 3.57	31.7 ± 3.60	32.2 ± 3.75	31.7 ± 3.55	31.8 ± 3.60	32.0 ± 3.92
Control	32.3 ± 4.79	32.9 ± 4.53	31.8 ± 4.26	31.0 ± 4.52	31.3 ± 4.26	31.1 ± 4.11	30.1 ± 2.58	30.7 ± 3.79
% HEX[b] (Mean ± SD)								
iStent *inject*	59.4 ± 5.96	57.8 ± 5.13	58.4 ± 5.50	59.5 ± 5.17	60.0 ± 5.46	60.5 ± 5.14	60.7 ± 5.65	61.1 ± 5.62
Control	59.6 ± 6.94	57.8 ± 5.10	58.8 ± 5.63	59.4 ± 7.02	59.8 ± 6.06	61.0 ± 5.01	61.6 ± 4.76	62.3 ± 5.96

CV = coefficient of variation; ECD = endothelial cell density; ECL = endothelial cell loss; HEX = percentage of hexagonal cells.

[a]One patient in the iStent *inject* group had CV >45 at 3 and 60 months; 1 patient in the control group had CV >45 at postoperative months 3, 6, 12, 18, and 24.

[b]The %HEX was <45% in 1 patient at 3, 6, and 18 months, and in 2 patients at 60 months postoperatively in the iStent *inject* group; the %HEX was <45% in 2 patients at 12 months postoperatively in the control group.

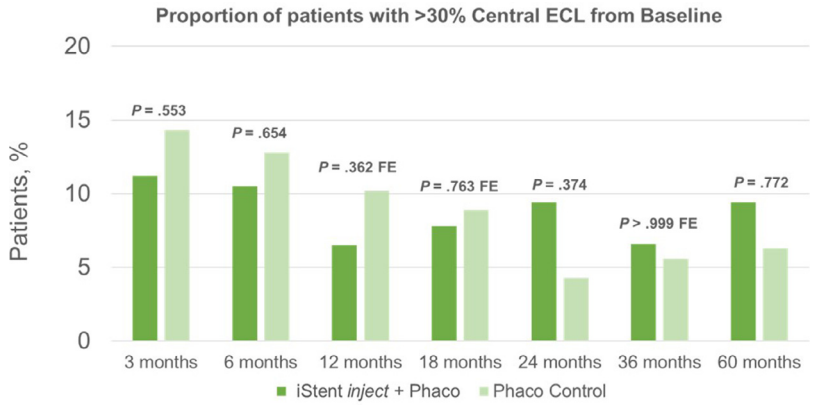

FIGURE 3. Five-year trend in the proportion of patients with >30% central endothelial cell loss from screening. No significant differences between the iStent *inject* group and control group were observed in the rate of endothelial cell loss >30% at any time point within the 60-month follow-up period. At 60 months, the rate of endothelial cell loss >30% was 9.4% and 6.3% in the iStent *inject* group and the control group, respectively ($P = .772$).

ferences between groups between 3 and 60 months postoperative; hence, iStent *inject* had no additional impact on ECL.

Both the ECD, CV, and HEX mean values were similar in the iStent *inject* and control groups at 60 months; for both groups, neither measure was significantly different at 60 months compared with screening values. In addition, no statistically or clinically significant differences were observed in the percentage of eyes with ECL >30% at the 60-month visit in the iStent *inject* group vs the control group. Overall, these results suggest that implantation of iStent *inject* does not lead to any additional adverse effect on ECD or ECL vs phacoemulsification alone over the long term.

These data can be considered in the context of long-term safety analyses of other MIGS devices, for example, Hydrus Microstent (Alcon) and CyPass Micro-Stent (Alcon). Following the 2-year time point, an additional 3-year follow-up on the Hydrus Microstent was conducted as part of the HORIZON study.[25] At month 3, there was a statistically significant difference in the proportion of study patients with >30% ECL (17.3% in Hydrus eyes vs 9.4% in control eyes; $P = .01$).[25,26] In addition, the 5-year HORIZON study showed statistically significant differences in mean ECD between the Hydrus group (1967 ± 522 cells/mm^2) and the control group (2117 ± 442 cells/mm^2; $P = .004$) at the 5-year follow-up. Furthermore, the proportion of patients with >30% ECL at 5 years postoperatively was greater in the Hydrus group than in the control group (20.8% vs 10.6%; $P = .011$, respectively) (Ahmed et al, presented at American Academy of Ophthalmology 2022 Virtual Meeting).[25] The authors noted that there was a comparable rate of ECL after 3 months for both groups, suggesting that the difference in ECL was attributable to the surgical trauma of Hydrus stent placement but with good tolerability thereafter.

Following the 2-year COMPASS trial,[24] a 3-year extension was completed for the CyPass Micro-Stent (COMPASS-XT trial).[15] The COMPASS-XT trial compared ECL after CyPass implantation with concomitant phacoemulsification to phacoemulsification alone. Results from the study showed a greater annualized rate of ECL, calculated from month 6 onward, in the implant group than in the control group, signifying additional impact from the device even after the initial surgical trauma. At 5 years, greater central ECL in the CyPass group was observed compared to the control group. Furthermore, the percentage of eyes with ECL >30% was 27.2% vs 10.0% in the CyPass group vs the control group, respectively. Changes in ECD and ECL at 60 months were predictable based on the position of the CyPass stent, with anterior placement and a greater number of visible rings, leading to greater ECL and lower ECD changes from baseline. Subsequently, CyPass was voluntarily removed from the world market because of the emergence of these safety concerns.[4]

In the 2-year[24] and 5-year[15] postoperative COMPASS studies, the mean percentage changes from baseline in ECD in the phacoemulsification-alone group were 9% (SD = 13%) and 10% (95% CI = 6.3%-13.9%), respectively, comparable to, at least the short-term, ECL in eyes without glaucoma undergoing phacoemulsification.[27-33] In our report, in the iStent *inject* phacoemulsification control group, the 2- and 5-year postoperative mean percentage decreases in ECD from screening were 11% ± 12% and 15% ± 10%, respectively. These findings support that with modern phacoemulsification, cataract removal can be successfully performed in the population with mild to moderate glaucoma with ECL comparable that in patients without glaucoma undergoing phacoemulsification.

In the current study, all participants from the 2-year trial were invited to continue into the extension follow-up. The original study population (n = 505 eligible) was narrowed to those participants completing the 60-month follow-up (n = 227). We addressed this potential source of selection bias by comparing key demographic, ocular, and ECD parameters at screening and 24 months in the patients who enrolled in the current extension study vs those who did not enroll. Although the 2 groups differed slightly in baseline VF and visual acuity, no study outcome–related differences between the groups in demographics, ECD, or change in ECD were found at screening or at 24 months that would suggest a risk of selection bias affecting study outcomes. A limitation of our study could be the degree of potential variability in longitudinal repeated imaging of the central endothelium and variability in ECD measurement between the reading center readers. These variabilities, however, were addressed and managed by analyzing 3 images in the central endothelial region and having an adjudication process if measurements differed by more than 5% between the 2 readers. Finally, most patients with mild to moderate POAG and age-related cataract are expected to have a longer average life expectancy than the 5-year follow-up period of this study; a longer follow-up period could capture any potential longer-term effects of iStent *inject* implantation on ECL, although this is unlikely given the stability of ECL beyond the 6-month postoperative period.

Albeit not studied in this trial, patients with mild to moderate glaucoma who are eligible for cataract surgery may have eyes with low preoperative ECD of <1500 cells/mm^2; thus, corneal endothelial safety plays an important role in the decision-making process for treatment selection. A key consideration of treatment for patients with glaucoma is to ensure that damage to the endothelial cell layer is minimized during intervention, especially because further intervention (with the potential to cause endothelial cell damage) may be required in the future. The results presented in the current study demonstrate that the implantation of iStent *inject* does not cause any further damage to the corneal endothelial cell layer beyond cataract surgery alone.

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