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Phase 3 Randomized Clinical Trial of the Safety and Efficacy of Travoprost Intraocular Implant in Patients with Open-Angle Glaucoma or Ocular Hypertension

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Purpose: To evaluate the safety and intraocular pressure (IOP)-lowering efficacy of 2 models of the travoprost intraocular implant (fast-eluting [FE] and slow-eluting [SE] types) from 1 of 2 phase 3 trials (the GC-010 trial).

Design: Multicenter, randomized, double-masked, sham-controlled, noninferiority trial.

Participants: Patients with open-angle glaucoma or ocular hypertension having an unmedicated baseline mean diurnal IOP (average of 8 AM, 10 AM, and 4 PM time points) of $\geq$ 21 mmHg, and IOP of $\leq$ 36 mmHg at each of the 8 am, 10 am, and 4 pm timepoints at baseline.

Methods: Study eyes were randomized to the travoprost intraocular implant (FE implant [n = 200] or SE implant [n = 197] model) or to timolol ophthalmic solution 0.5% twice daily (n = 193).

Main Outcome Measures: The primary outcome was mean change from baseline IOP in the study eye at 8 AM and 10 AM, at each of day 10, week 6, and month 3. Safety outcomes included adverse events (AEs) and ophthalmic assessments.

Results: Mean IOP reduction from baseline over the 6 time points ranged from 6.6 to 8.4 mmHg for the FE implant group, from 6.6 to 8.5 mmHg for the SE implant group, and from 6.5 to 7.7 mmHg for the timolol group. The primary efficacy end point was met; the upper limit of the 95% confidence interval of the difference between the implant groups and the timolol group was $<$ 1 mmHg at all 6 time points. Study eye AEs, most of mild or moderate severity, were reported in 21.5%, 27.2%, and 10.8% of patients in the FE implant, SE implant, and timolol groups, respectively. The most common AEs included iritis (FE implant, 0.5%; SE implant, 5.1%), ocular hyperemia (FE implant, 3.0%; SE implant, 2.6%), reduced visual acuity (FE implant, 1.0%; SE implant, 4.1%; timolol, 0.5%), and IOP increased (FE implant, 3.5%; SE implant, 2.6%; timolol, 2.1%). One serious study eye AE occurred (endophthalmitis).

Conclusions: The travoprost intraocular implant demonstrated robust IOP reduction over the 3-month primary efficacy evaluation period after a single administration. The IOP-lowering efficacy in both implant groups was statistically and clinically noninferior to that in the timolol group, with a favorable safety profile.

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Several groundbreaking, randomized controlled clinical trials have demonstrated that reducing intraocular pressure (IOP) can delay or prevent the onset of glaucomatous visual field loss.[1–6] Elevated IOP, the only known modifiable risk factor, can be treated with medical therapy, laser therapy, or incisional surgery (alone or in combination). Medical therapy traditionally has served as the initial intervention to lower IOP, with a variety of medication classes available that differ in their method of action, IOP-lowering efficacy, dosing frequency, side effects, and potential contraindications to use. Prostaglandin analogs (PGAs) are the most commonly used topical IOP-lowering medications owing to their excellent IOP-lowering efficacy with a once-daily dosing regimen and well-established safety profile. However, adherence to topical IOP-lowering medication notoriously is poor for a number of factors, including inability to instill eyedrops effectively and accurately, difficulty with remembering medication regimens with multiple

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medications, different dosing schedules, and undesirable side effects (e.g., ocular surface disease, conjunctival hyperemia).[7–12] Nearly 50% of patients discontinue the initially prescribed topical IOP-lowering medications completely within 6 months, and some 90% of patients intermittently fail to refill the prescriptions over a 3-year period.[8] Poor adherence to topical IOP-lowering medication has been shown to be associated with glaucomatous visual field progression.[13,14]

Sustained-release drug delivery systems that are readministered periodically have the potential to alleviate the issue of poor adherence. In this regard, the travoprost intraocular implant (Glaukos Corporation) is a novel delivery system consisting of a titanium implant reservoir, with a membrane that controls the sustained release of a proprietary formulation of travoprost. Two models of the travoprost intraocular implant, a fast-eluting (FE) model and a slow-eluting (SE) model, have been developed that differ in the thickness of the membrane, with the SE implant having the thicker membrane. The implant is preloaded in a sterile single-use inserter, is administered intracamerally through a small, clear corneal incision, and is anchored into the sclera at the iridocorneal angle.

A 3-year, phase 2 clinical trial demonstrated that both models of the travoprost intraocular implant were well tolerated and reduced topical IOP-lowering medication burden in a substantial percentage of implant patients. At 36 months, 63% and 69% of patients in the FE and SE implant groups, respectively, showed well-controlled IOP with the same number of or fewer topical IOP-lowering medications compared with the number used at screening.[15]

Two ongoing phase 3 clinical trials (the GC-010 and GC-012 trials; ClinicalTrials.gov identifiers, NCT03519386 and NCT03868124, respectively) are evaluating the efficacy and safety of the two models of the travoprost intraocular implant 75 μg compared with timolol 0.5% administered twice daily in patients with open-angle glaucoma or ocular hypertension for 3 years. Despite a better benefit-to-risk profile for the SE implant versus FE implant in the phase 2 trial, both implant models were studied in the phase 3 trials because of the United States Food and Drug Administration (FDA) requirement to include 2 implant arms for masking purposes. The results of the primary efficacy end point and safety of the implant through month 3 in the first of the two phase 3 trials (GC-010) are presented herein.

Methods

Study Design and Setting

This was a phase 3, parallel-group, double-masked (patient and observer), randomized, sham-controlled trial conducted in 44 clinical sites in the United States and 1 site in the Philippines (Appendix 1, available at https://www.aaojournal.org). Institutional review board or independent ethics committee approval (Western Institutional Review Board for 43 sites, Wills Eye Hospital Institutional Review Board for 1 site, and St. Cabrini Medical Center-Asian Eye Institute Ethics Review Committee for 1 site) was obtained for the trial, and patients provided written informed consent before undertaking any study-related procedures. The clinical trial was registered at ClinicalTrials.gov (identifier, NCT03519386) and was conducted in accordance with good clinical practices and the tenets of the Declaration of Helsinki.

Participants

The trial enrolled adult patients ≥ 18 years of age with a diagnosis of open-angle glaucoma (primary, pseudoexfoliative, or pigmentary) or ocular hypertension using 0 to 3 IOP-lowering medications at the screening visit. Patients were required to have a best spectacle-corrected visual acuity of 20/80 or better in each eye, a central corneal thickness of between 440 and 620 μm in the study eye, and an open anterior chamber angle (≥ 3 Schaffer angle at the planned implantation site) with absence of peripheral anterior synechia, rubeosis, or other angle abnormalities that could impede proper placement of the implant in the study eye.

Patients receiving no IOP-lowering medication at the screening visit were required to have an IOP of ≥ 21 mmHg and ≤ 36 mmHg in the study eye. No IOP criterion was applied to patients receiving IOP-lowering medication at the screening visit; however, they were ineligible for washout if, in the opinion of the investigator, the unmedicated IOP in the study eye was expected to exceed 36 mmHg. At the baseline visit, all patients were required to have a unmedicated mean diurnal IOP (average of 8 AM, 10 AM, and 4 PM IOP) of ≥ 21 mmHg and to have an IOP ≤ 36 mmHg at each of the 3 diurnal time points after washout from IOP-lowering medication, if applicable, in the study eye. Minimum washout duration was 8 weeks for ρ-kinase inhibitors, 4 weeks for β-blockers and PGAs, 3 weeks for α-agonists, 7 days for carbonic anhydrase inhibitors, and 5 days for miotics. If both eyes qualified at screening, the investigator could choose to implement a bilateral washout. If both eyes qualified at baseline, the right eye was to be selected as the study eye.

Key exclusion criteria included traumatic, uveitic, neovascular, or angle-closure glaucoma or glaucoma associated with vascular disorders; visual field mean deviation worse than −12 dB or functionally significant visual field loss; cup-to-disc ratio > 0.8; previous incisional glaucoma surgery or argon laser trabeculoplasty; history of iridotomy, selective laser trabeculoplasty, or micropulse laser trabeculoplasty within the prior 90 days; active corneal inflammation or edema; clinically significant corneal dystrophy or guttata; significant scarring or irregularities that could interfere with reliable IOP measurement; anticipated corneal refractive surgery or corneal opacities or disorders that could inhibit visualization of the nasal angle; visually significant cataract or congenital or traumatic cataract; choroidal detachment, effusion, choroiditis, neovascularization, or any active choroidopathy; retinal or optic nerve disorders that were not associated with the existing glaucoma; or any other ocular disease or condition that would place the patient at risk from participation in the trial.

In addition, patients were excluded if they had uncontrolled systemic disease or an immunodeficiency condition, used a systemic carbonic anhydrase inhibitor within the 30 days before the screening visit, had a known allergy or hypersensitivity to the study medications or their components, used a systemic steroid within 30 days before the screening visit or anticipated use of a steroid during the course of the study, or had a change in an existing chronic systemic therapy that could substantially affect IOP or the study outcomes within 30 days before the screening visit or anticipated a change in such therapy during the course of the study. Finally, women of childbearing potential were required to have negative pregnancy test results before enrollment and were excluded from participation if they were pregnant or planning to become pregnant during the course of the study.

Randomization and Masking

Treatment assignment was via interactive response technology. Randomization was in a 1:1:1 treatment allocation into 3 groups receiving the FE implant, the SE implant, or timolol and was stratified based on baseline unmedicated mean diurnal IOP ($\leq$ 25 mmHg vs. $>$ 25 mmHg). Randomization assignment, which corresponded to a unique kit number, was obtained by the surgeon (or designee) immediately before the surgical procedure. Study participants, examiners assessing IOP, reading center graders (for central corneal endothelial cell count), and the sponsor personnel were masked to treatment assignment. Intraocular pressure was assessed by Goldmann applanation tonometer using a 2-examiner technique in which one examiner unmasked to treatment viewed through the biomicroscope and turned the dial while the second examiner masked to treatment recorded the readings.

An unmasked surgeon administered the FE or SE travoprost intraocular implant (which were identical in appearance to aid with masking) or performed a sham surgical procedure using the tip of a sterile tuberculin syringe. Patients who received an implant received a 0.01% benzalkonium chloride-preserved artificial tear solution (Advanced Eye Relief Dry Eye Rejuvenation; Bausch & Lomb) to be administered twice daily to the study eye, and those receiving a sham procedure received 0.01% benzalkonium chloride-preserved timolol maleate ophthalmic solution USP (United States Pharmacopeia) 0.5% (Akorn, Inc or Sandoz) to be administered twice daily to the study eye. Bottles of artificial tear and timolol solutions had identical masked labeling and yellow cap color.

Procedures and Assessments

Before surgery, a topical fourth-generation fluoroquinolone antibiotic was used prophylactically for ocular infection. Patients were instructed to instill the medication 4 times daily for at least 1 day before surgery in the study eye. In cases of allergy or contraindication to fluoroquinolone antibiotics, polymyxin B sulfate plus trimethoprim sulfate ophthalmic solution USP was used instead.

On the day of surgery, an additional drop of antibiotic was administered 30 minutes before surgery. An anesthetic (general, retrobulbar, peribulbar, or topical for patients receiving an implant; topical for patients undergoing the sham procedure) was administered before performing the implantation or sham procedure.

In addition to masked study medication, a topical nonsteroidal anti-inflammatory drug was to be instilled in the study eye for 1 week after the procedure, according to the dosage and frequency recommended by the manufacturer, and a topical fluoroquinolone antibiotic (or polymixin B sulfate plus trimethoprim ophthalmic solution) was to be administered 4 times daily for 1 week or at the discretion of the investigator.

Postoperative study visits occurred 1 to 2 days after surgery, as well as at day 10, week 4, week 6, and month 3. Assessments included visual acuity, slit-lamp biomicroscopy, conjunctival hyperemia and iris color assessment, specular microscopy (at select sites in a small subset of patients), IOP, and gonioscopy.

If IOP increased to $\geq$ 30 mmHg within 2 days after surgery, the investigator could institute medical treatment and paracentesis (the latter, if necessary, in eyes that received an implant). If IOP increased to $>$ 22 mmHg at day 3 or later, IOP was to be rechecked within 7 days. If rechecked IOP was $>$ 25 mmHg or if the IOP reduction was $<$ 20% compared with baseline IOP, additional IOP-lowering medication was to be prescribed for the study eye, preferably a topical carbonic anhydrase inhibitor. The fellow eye was treated outside the parameters of the study, with timolol-containing eye drops used as a concomitant medication in 25.0%, 21.3%, and 27.5% of fellow eyes of patients in the FE implant, SE implant, and timolol groups, respectively.

Outcomes

The primary efficacy end point, as required by the United States FDA for approval of a New Drug Application for an IOP-lowering medication, was the mean change from baseline in IOP at the 8 AM and 10 AM time points at day 10, week 6, and month 3. The main safety outcomes were the incidence of study eye adverse events (AEs) and non−study eye ocular and nonocular AEs. Adverse events were judged by the investigator as related (possibly, probably, or definitely) or unrelated (unlikely or definitely) to study treatment and according to severity (mild, moderate, or severe). Other safety measures included visual acuity, ocular parameters evaluated by slit-lamp biomicroscopy, conjunctival hyperemia assessment, and gonioscopy. Hyperemia was scored on a photographic 5-point grading scale: 0 indicating normal, 0.5 indicating trace, 1 indicating mild, 2 indicating moderate, and 3 indicating severe.

Statistical Analysis

The sample size estimate was based on a noninferiority test of the difference between the SE and FE implant groups versus the timolol 0.5% group, assuming a standard deviation of 3.0 for the timolol control group and 4.0 for the implant groups; normal distributions for the IOP measurements at 8 AM and 10 AM at day 10, week 6, and month 3; a 1-sided α value of 0.025; and noninferiority margins of 1.5 mmHg at all time points and 1.0 mmHg at $\geq$ 3 time points. With a true mean difference of 0, 85% power to declare noninferiority for at least 1 implant group over the timolol group would be achieved with 186 patients per treatment group or 558 patients overall.

To control the overall type I error at 0.05 level for comparing the two implant groups with the timolol group, a fixed sequence hierarchical testing procedure was used while accounting for testing both the FE and SE implant groups using 2-sided 95% confidence intervals (CIs) at each level. Testing for noninferiority of the SE implant to timolol was conducted first, and, if noninferiority was demonstrated, then testing for noninferiority of the FE implant to timolol was undertaken. The primary end point was the difference between the implant groups and timolol group in mean change from baseline in mean diurnal IOP (average of the 8 AM and 10 AM time points) at the day 10, week 6, and month 3.

The primary analysis of the primary end point used an analysis of covariance (ANCOVA) model that included treatment as the main effect and baseline as a covariate accounted for additional IOP-lowering medication at the visit level and imputed missing data using a worse-half method. The analysis was performed on the intention-to-treat (ITT) analysis set, which comprised all randomized patients, with analyses performed according to original treatment assignment, regardless of actual treatment received.

Sensitivity analyses for the primary end point were performed as follows: ANCOVA with the worse-half imputation method for timolol accounting for additional IOP-lowering medication use at the visit level on the ITT analysis set; ANCOVA with the worse-half imputation method accounting for additional IOP-lowering medication use at the visit level on the per-protocol analysis set; ANCOVA with the worse-half imputation method accounting for additional IOP-lowering medication use at the study level (i.e., as soon as a patient was receiving additional IOP-lowering medication after day 5, the patient was always counted as receiving additional IOP-lowering medication) on the ITT analysis set; ANCOVA based on observed case on the ITT analysis set; ANCOVA based on last observation carried forward on the ITT

analysis set; a permutation test using the trimmed mean method accounting for additional IOP-lowering medication use at the visit level on the ITT analysis set; and a tipping point analysis in which the treatment effect was re-evaluated after adding a successively more extreme shift parameter to the values for implant patients with imputed data. Analyses also were performed for the primary end point using an ANCOVA, with the worse-half imputation method accounting for additional IOP-lowering medication use at the visit level on the ITT analysis set for the following subgroups: (1) patients with baseline unmedicated mean diurnal IOP of $\leq$ 25 mmHg versus $>$ 25 mmHg, (2) patients receiving 0 or 1 versus 2 or 3 IOP-lowering medication class(es) at screening, and (3) patients who did not receive timolol in the fellow eye. Finally, an ad hoc sensitivity analysis was performed on the change from baseline in mean diurnal IOP using 9 time points (8 AM, 10 AM, and 4 PM at each of the day 10, week 6, and month 3 time points) using an ANCOVA with the worse-half imputation method accounting for additional IOP-lowering medication use at the visit level and at the study level on the ITT analysis set.

The per-protocol analysis set, which was used for selected sensitivity analyses on the primary end point, included all patients in the ITT group who received study treatment based on the randomization schedule and who did not have major protocol deviations likely to impact the primary efficacy end points. Major protocol deviations were determined before database lock.

A prespecified analysis also was performed on the percentage of patients who received additional IOP-lowering medication using the ITT analysis set and counting patients receiving additional IOP-lowering medication separately at the visit level. Responder analyses also were performed on the percentage of patients achieving an IOP reduction from baseline of at least 25%, the percentage achieving an IOP reduction from baseline of at least 8 mmHg, and the percentage achieving an IOP reduction of $\leq$ 18 mmHg. No multiplicity adjustments were made for these analyses. All analyses were performed using SAS for Windows version 9.4 (SAS Institute, Inc.).

Safety analyses were conducted on the safety analysis set, which comprised all patients who were randomized and received at least 1 dose of study treatment. If patients were misrandomized or received incorrect study treatment, they were grouped according to the actual treatment they received. Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities version 21.0 in English. Adverse events were classified into ocular AEs and nonocular or non−study eye AEs.

For best spectacle-corrected visual acuity, the actual value and change from baseline in number of letters read correctly were calculated for each visit after baseline and were summarized as continuous variables by treatment group. For conjunctival hyperemia, the number and percentage of patients in each severity grade were summarized by treatment group and visit for the study eye.

For corneal endothelial cell counts, the actual change from baseline, and percent change from baseline in central endothelial cell counts were calculated for each visit after baseline and were summarized by treatment group. In addition, the number and percentage of patients with $\geq$ 30% loss from baseline in central endothelial cell counts were summarized by treatment group.

Results

Demographics and Baseline Characteristics

Between May 2018 and March 2021, a total of 954 patients were screened, of whom 364 patients were not randomized because of failure to meet inclusion or exclusion criteria or both at screening or baseline. Of those screened, 590 eligible patients were randomized to 1 of 3 treatment groups: 200 patients in the FE implant group, 197 patients in SE implant group, and 193 patients in the timolol group. A total of 589 patients received study treatment and were included in the safety analyses. Four patients received study treatment that differed from that to which they were randomized: 1 patient randomized to FE implant received timolol, 1 patient randomized to timolol received an FE implant, 1 patient randomized to the SE implant received timolol, and 1 patient randomized to the SE implant received an FE implant. In addition, 1 patient randomized to the FE implant group did not receive an implant. Patient disposition is shown in Table 1. A total of 580 of 590 patients (98.3%) completed 3 months of the study.

Patient demographics and baseline characteristics are shown in Table 2. The baseline unmedicated mean diurnal IOP was 24.2 $\pm$ 2.8 mmHg in the FE implant group, 24.0 $\pm$ 2.8 mmHg in the SE implant group, and 24.1 $\pm$ 2.7 mmHg in the timolol group. The distribution of patients in the baseline unmedicated mean diurnal IOP strata ($\leq$ 25 mmHg or $>$ 25 mmHg) was similar in the 3 treatment groups. Demographics and baseline characteristics were well balanced across treatment groups. An exception was corneal endothelial cell count (which was collected in a subset of patients), which was notably lower at baseline in the FE implant group (2230.55 cells/mm^2) than in the SE implant (2403.95 cells/mm^2) and timolol (2445.49 cells/mm^2) groups.

Efficacy

The unmedicated mean IOP in study eyes was well balanced across the treatment groups at baseline (Table 2). Mean IOP values at screening and at the 8 AM time point at baseline, day 10, week 6, and month 3 are shown in Figure S1 (available at www.aaojournal.org).

Robust IOP reductions from baseline were achieved at all visits and time points. The magnitude of the change from baseline in diurnal IOP (measured at the 8 AM and 10 AM time points) in study eyes consistently was greater in the implant groups compared with the timolol group for both time points at day 10 and week 6 and for 1 of the 2 time points at month 3. Across the 6 time points, the IOP changes from baseline ranged from −6.6 to −8.4 mmHg in the FE implant group, from −6.6 to −8.5 mmHg in the SE implant group, and from −6.5 to −7.7 mmHg in the timolol group (Fig 2A). The differences in IOP change from baseline at the 6 time points for the FE implant and SE implant groups versus the timolol group are shown in Table 3.

The maximal mean difference in IOP change from baseline across all 6 time points was 0.10 mmHg (with an upper 95% CI of 0.83 mmHg) for the FE implant versus timolol groups and 0.10 mmHg (with an upper 95% CI of 0.82 mmHg) for the SE implant versus timolol groups. Therefore, the criteria for statistical and clinical noninferiority to timolol was met for both implant groups because the upper limit of the 95% CI of the difference between the implant groups and the timolol group was $<$ 1.5 mmHg and also $<$ 1 mmHg for all 6 time points (Table 3).

All of the sensitivity analyses using various ANCOVA methods, and the permutation test method supported the results of the primary analysis and demonstrated statistical and clinical noninferiority of both the FE and SE implants to timolol (Table S4, available at www.aaojournal.org). The tipping point sensitivity analysis revealed that the shift parameter required no longer to demonstrate noninferiority to timolol was $\geq$ 6.1 mmHg for the FE and SE implants, thereby indicating the robustness of the study outcome to the underlying assumptions of missing data and data after intercurrent events. Results for the ANCOVA on the ITT analysis using observed cases are shown in Figure 2B.

Table 1. Patient Disposition

Variable	Fast-Eluting Implant	Slow-Eluting Implant	Timolol
Randomized	200	197	193
Intention-to-treat set	200 (100)	197 (100)	193 (100)
Safety set	200 (100)	195 (99.0)	194 (100.5)
Per-protocol set	197 (98.5)	194 (98.5)	192 (99.5)
Completed month 3	196 (98.0)	195 (99.0)	189 (97.9)
Discontinued before or at month 3	2 (1.0)	1 (0.5)	4 (2.1)
Withdrew consent	1 (0.5)	0	0
Investigator decision	1 (0.5)	0	0
Lost to follow-up	0	1 (0.5)	0
Death	0	0	2 (1.0)
Adverse event	0	0	2 (1.0)
Other	0	0	0

Data are presented as no. of patients (%). Four patients were assigned kits at the operative visit that differed from those to which they were randomized. One patient randomized to the fast-eluting implant failed to receive an implant.

Statistical and clinical noninferiority of the implant groups to timolol also was demonstrated in ad hoc sensitivity analyses of the change from baseline in diurnal IOP using the 9 time points (i.e., 8 AM, 10 AM, and 4 PM time points at day 10, week 6, and month 3). The upper limit of the 95% CI of the difference between the implant groups and the timolol group was < 1.5 mmHg and also $<$ 1 mmHg for all 9 time points in analyses using ANCOVA on the ITT analysis set, with the worse-half imputation method accounting for additional IOP-lowering medication use at the visit level and accounting for additional IOP-lowering medication use at the study level (Table S5, available at www.aaojournal.org).

Robust IOP reductions from baseline were observed in the subgroups of patients based on baseline unmedicated mean diurnal IOP strata (≤ 25 mmHg and > 25 mmHg), as well as based on the number of IOP-lowering medication classes at screening (0−1 and 2−3; Table S6, available at www.aaojournal.org). Statistical and clinical noninferiority of both the FE and SE implant groups to the timolol group was demonstrated for the subgroup of patients with baseline unmedicated mean diurnal IOP of ≤ 25 mmHg and in the subgroup of patients receiving 0 or 1 IOP-lowering medication class at screening. Statistical and clinical noninferiority of the SE implant group to the timolol group also was demonstrated in the subgroup of patients receiving 2 or 3 IOP-lowering medication classes at screening.

In addition, robust statistical and clinical noninferiority to the timolol group was demonstrated for the subgroup of patients who received FE or SE implants not using timolol in the fellow eye, thus confirming that noninferiority of the travoprost implants to timolol was not dependent on the crossover IOP-lowering effect of timolol administered to the nonstudy fellow eye of implant patients (Table S7, available at www.aaojournal.org).

The IOP-lowering efficacy of the implants was evaluated further by separate analyses of the percentage of study eyes achieving an IOP reduction from baseline of at least 25% (Fig 3A), the percentage of study eyes achieving an IOP reduction from baseline of at least 8 mmHg (Fig 3B), and the percentage of study eyes achieving an IOP of ≤ 18 mmHg (Fig 3C). The 8-mmHg response criterion was based on the IOP reduction typically achieved by topical PGAs[16–18]; a target IOP of $\leq$ 18-mmHg response criterion often is the goal for patients with mild to moderate glaucoma and is based on an IOP level associated with a reduced progression of glaucomatous visual field defects.[4,5] These analyses showed that most patients achieved clinically relevant IOP reductions through the 3-month evaluation period. At the 8 AM time point of month 3, 55.5%, 55.3%, and 56.0% of patients in the FE implant, SE implant, and timolol groups, respectively, achieved a $\geq 25\%$ IOP reduction from baseline. At the 10 AM time point, the percentages were 56.5%, 54.8%, and 57.0% patients in the FE implant, SE implant, and timolol groups, respectively. At the 8 AM time point of month 3, 36.0%, 37.1%, and 38.3% of patients in the FE implant, SE implant, and timolol groups, respectively, achieved an $\geq$ 8-mmHg response. At the 10 AM time point, the percentages were 36.0%, 39.6%, and 35.8% of patients in the FE implant, SE implant, and timolol groups, respectively. Finally, at the 8 AM time point of month 3, 58.0%, 55.8%, and 59.1% of patients in the FE implant, SE implant, and timolol groups, respectively, achieved an IOP of $\leq$ 18 mmHg. At the 10 AM time point, the percentages were 59.5%, 61.4%, and 61.1% of patients in the FE implant, SE implant, and timolol groups, respectively.

An analysis of the percentage of patients who received additional topical IOP-lowering medication(s) for the study eye, when counting patients receiving additional IOP-lowering medication separately at the visit level, demonstrated that at month 3, 5.1% of patients in the FE implant group, 4.2% of patients in the SE implant group, and 7.0% of patients in the timolol group were receiving additional topical IOP-lowering medication (Fig S4, available at www.aaojournal.org).

Safety

Two deaths, both the result of nonocular AEs (cardiorespiratory arrest and coronavirus infection) occurred in the timolol group (1.0%) during the 3-month evaluation period. No deaths were reported in either implant group. Discontinuations because of treatment-related AEs were reported in 2 patients in the timolol group (1.0%; moderate dermatitis contact and moderate hypersensitivity to study drops in 1 patient each). No AEs leading to discontinuation were reported in the implant groups.

Nonocular serious AEs, none of which were considered related to study treatment, were reported in 5 patients (2.6%) in the SE implant group (electrolyte imbalance, lumbar spinal stenosis, atrial fibrillation, and nephrolithiasis in 1 patient each and cardiac valve disease, coronary artery occlusion, and myocardial infarction in 1 patient each) and in 4 patients (2.1%) in the timolol group (chest pain, cardiorespiratory arrest, bipolar disorder, and coronavirus infection in 1 patient each). No nonocular serious AEs occurred in the FE implant group.

Nonocular or non−study eye AEs considered related to study treatment were reported in 1 patient in each of the FE implant (moderate headache) and SE implant (mild rhinorrhea) groups. No treatment-related nonocular or non−study eye AEs occurred in the timolol group.

An ocular serious AE was reported in 1 patient (0.5%) in the SE implant group. Endophthalmitis, which was severe and considered to be related to study treatment, was diagnosed on study day 8. The eye was treated with intraocular antibiotics and the endophthalmitis resolved with sequelae (worsening of cataract, posterior synechiae) by study day 29. No ocular serious AEs occurred in the FE implant or timolol groups.

Study eye AEs were reported in 43 patients (21.5%), 53 patients (27.2%), and 21 patients (10.8%) in the FE implant, SE implant, and timolol groups, respectively. The most frequent AEs reported at an incidence of $\geq 3\%$ in any treatment group included iritis, ocular hyperemia, reduced visual acuity, and increased IOP (Table 8).

Table 2. Patient Demographics and Baseline Characteristics

Characteristic	Fast-Eluting Implant	Slow-Eluting Implant	Timolol
Age			
No.	200	197	193
Mean ± SD, yrs	63.8 ± 11.5	63.2 ± 12.6	63.8 ± 11.4
Age category			
≥ 18 to < 65 yrs	102 (51.0)	91 (46.2)	93 (48.2)
≥ 65 yrs	98 (49.0)	106 (53.8)	100 (51.8)
Sex			
Male	91 (45.5)	98 (49.7)	85 (44.0)
Female	109 (54.5)	99 (50.3)	108 (56.0)
Race			
White	143 (71.5)	120 (60.9)	128 (66.3)
Black or African American	38 (19.0)	50 (25.4)	41 (21.2)
Asian	15 (7.5)	19 (9.6)	16 (8.3)
Native Hawaiian or other Pacific Islander	1 (0.5)	0	0
American Indian or Alaska Native	0	0	2 (1.0)
Other	3 (1.5)	7 (3.6)	5 (2.6)
Unknown	0	1 (0.5)	1 (0.5)
Ethnicity			
Hispanic or Latino	9 (4.5)	15 (7.6)	10 (5.2)
Not Hispanic or Latino	191 (95.5)	179 (90.9)	180 (93.3)
Unknown	0	3 (1.5)	3 (1.6)
Type of disease			
Open-angle glaucoma	175 (87.5)	170 (86.3)	167 (86.5)
Ocular hypertension	25 (12.5)	27 (13.7)	26 (13.5)
No. of IOP-lowering medication classes at screening			
0	43 (21.5)	54 (27.4)	46 (23.8)
1	116 (58.0)	99 (50.3)	100 (51.8)
2	37 (18.5)	38 (19.3)	41 (21.2)
3*	4 (2.0)	6 (3.0)	6 (3.1)
Screening IOP, mmHg			
No.	200	197	193
Mean ± SD	19.52 ± 4.50	19.77 ± 4.46	19.67 ± 4.35
Baseline unmedicated mean diurnal IOP, mmHg			
No.	200	197	193
Mean ± SD	24.18 ± 2.78	24.02 ± 2.81	24.12 ± 2.68
Baseline unmedicated mean diurnal IOP strata, mmHg			
≤ 25	141 (70.5)	141 (71.6)	138 (71.5)
> 25	59 (29.5)	56 (28.4)	55 (28.5)
Lens status			
No.	200	195	194
Phakic	137 (68.5)	140 (71.8)	130 (67.0)
Pseudophakic	63 (31.5)	55 (28.2)	64 (33.0)
Central endothelial cell count†			
No.	26	20	20
Mean ± SD, cells/mm^2	2230.55 ± 493.90	2403.95 ± 472.25	2445.49 ± 282.23
Visual field mean deviation			
No.	200	195	194
Mean ± SD, dB	−1.905 ± 2.932	−1.719 ± 2.861	−1.866 ± 3.030
Vertical cup-to-disc ratio			
No.	200	195	194
Mean ± SD	0.54 ± 0.17	0.56 ± 0.18	0.57 ± 0.16
Central corneal thickness, μm			
No.	200	195	194
Mean ± SD	554.0 ± 36.3	550.3 ± 35.7	552.5 ± 36.4

IOP = intraocular pressure; SD = standard deviation.
Data are presented as no. (%), unless otherwise indicated. No statistical analyses were performed to compare treatment group demographic or baseline characteristics. Data for lens status, central endothelial cell count, visual field mean deviation, vertical cup-to-disc ratio, and central corneal thickness are based on the safety analysis set; all others are based on the intention-to-treat analysis set.
*The protocol initially permitted patients to qualify for eligibility if receiving 0 to 3 IOP-lowering medication classes at the screening visit, but was amended (January 2019) to allow a maximum of 2 medication classes.
†Measured on a subset of patients.

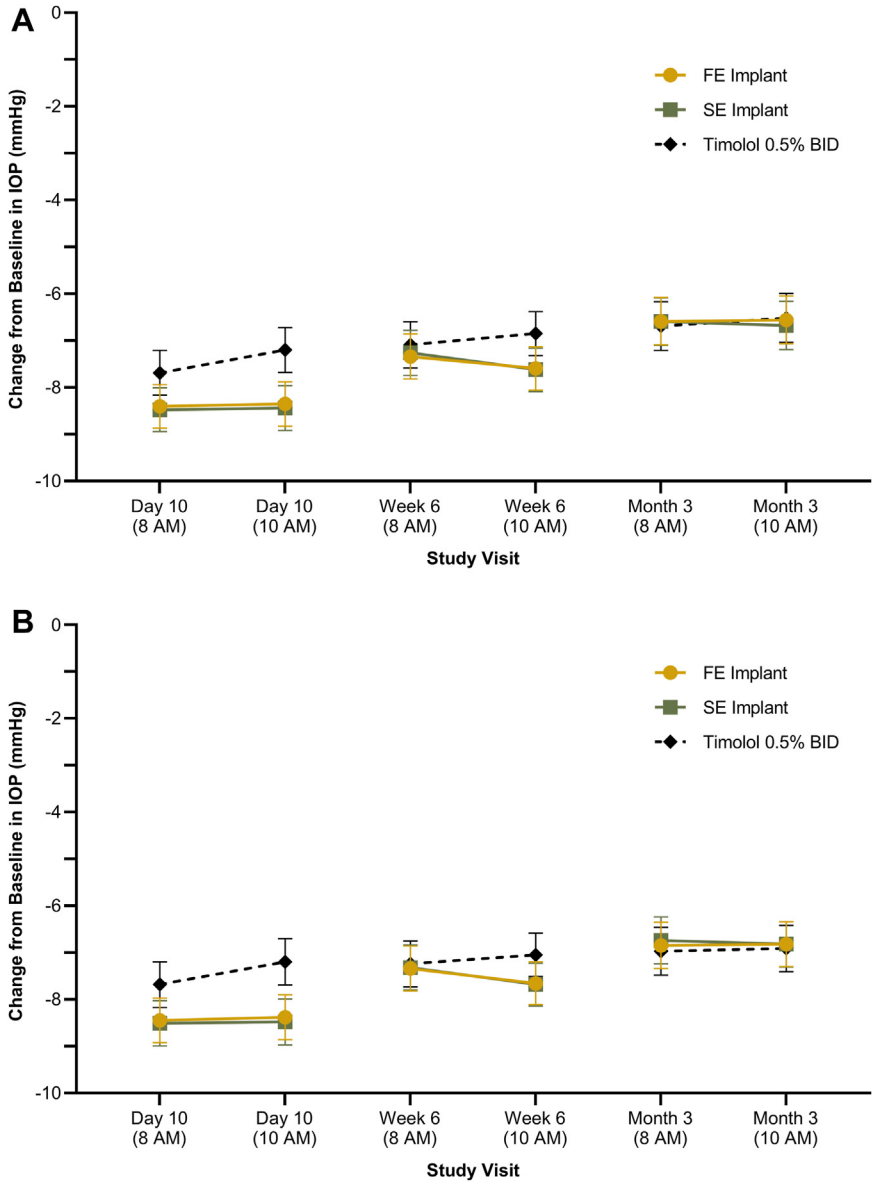

Figure 2. Graphs showing the mean change from baseline in intraocular pressure (IOP; measured in millimeters of mercury) for the fast-eluting (FE) implant, slow-eluting (SE) implant, and timolol 0.5% twice daily (BID) treatment groups by visit and time of day across the 3-month period. Values represent the least square means ± 95% confidence interval from the time-matched baseline IOP. **A**, Worse-half method for multiple imputation, counting patients receiving additional IOP-lowering medication at the visit level. **B**, Observed case with no imputation of data.

Iritis was reported in 1 patient in the FE implant group and 10 patients in the SE implant group. Most of the AEs of iritis were mild or moderate (2 were severe), and all were considered related to study treatment. No AEs of iritis occurred in the timolol group.

Ocular hyperemia was reported in 6 patients in the FE implant group and 5 patients in the SE implant group. Most patients had mild or moderate ocular hyperemia (only 1 patient, in the FE implant group, had severe ocular hyperemia). Ocular hyperemia that was considered related to study treatment was reported in 6 of the 11 patients. No AEs of ocular hyperemia occurred in the timolol group.

Reduced visual acuity was reported in 2 patients in the FE implant group, 8 patients in the SE implant group, and 1 patient in the timolol group based on guidance provided to the investigators that a reduction from baseline of $\geq$ 10 letters was to be reported as an AE. Most of these patients experienced mild or moderate AEs of reduced visual acuity; events were severe in 1 patient in the FE implant group and in 2 patients in the SE implant group. In addition, in most patients who experienced reduced visual acuity, the AE was considered to be related to study treatment, apart from 1 patient each in the FE implant and timolol groups and 2 patients in the SE implant group.

Intraocular pressure increase was reported in 7 patients in the FE implant group, 5 patients in the SE implant group, and 4 patients in the timolol group. Most patients experienced mild or moderate IOP increase; severe events were reported in 2 patients in each of the implant groups and in no patients in the timolol group. Most events in the implant groups were considered related to study

Table 3. Change from Baseline in Intraocular Pressure (in Millimeters of Mercury) at 8 AM and 10 AM at Day 10, Week 6, and Month 3

Visit	Hour (AM)	Statistic	Fast-Eluting Implant (n = 200)	Slow-Eluting Implant (n = 197)	Timolol (n = 193)	Difference (95% Confidence Interval)	
						Fast-Eluting Implant vs. Timolol	*Slow-Eluting Implant vs. Timolol*
Day 10	8	No.	200	197	193		
		LS mean (SE)	−8.40 (0.24)	−8.48 (0.24)	−7.69 (0.24)	−0.72 (0.34)	−0.79 (0.34)
		95% CI	−8.87 to −7.94	−8.94 to −8.01	−8.16 to −7.21	−1.38 to −0.06	−1.45 to −0.13
	10	No.	200	197	193		
		LS mean (SE)	−8.35 (0.24)	−8.44 (0.24)	−7.20 (0.24)	−1.15 (0.34)	−1.24 (0.34)
		95% CI	−8.83 to −7.88	−8.92 to −7.96	−7.68 to −6.72	−1.83 to −0.48	−1.92 to −0.56
Week 6	8	No.	200	197	193		
		LS mean (SE)	−7.34 (0.24)	−7.26 (0.25)	−7.09 (0.25)	−0.25 (0.35)	−0.18 (0.35)
		95% CI	−7.82 to −6.86	−7.74 to −6.78	−7.58 to −6.60	−0.93 to 0.43	−0.86 to 0.51
	10	No.	200	197	193		
		LS mean (SE)	−7.59 (0.24)	−7.62 (0.24)	−6.85 (0.24)	−0.74 (0.34)	−0.77 (0.34)
		95% CI	−8.06 to −7.13	−8.09 to −7.16	−7.32 to −6.38	−1.40 to −0.08	−1.43 to −0.11
Month 3	8	No.	200	197	193		
		LS mean (SE)	−6.59 (0.26)	−6.59 (0.26)	−6.69 (0.27)	0.10 (0.37)	0.10 (0.37)
		95% CI	−7.09 to −6.08	−7.10 to −6.09	−7.21 to −6.17	−0.62 to 0.83	−0.63 to 0.82
	10	No.	200	197	193		
		LS mean (SE)	−6.56 (0.26)	−6.68 (0.26)	−6.52 (0.27)	−0.04 (0.37)	−0.16 (0.37)
		95% CI	−7.07 to −6.05	−7.19 to −6.16	−7.04 to −5.99	−0.77 to 0.69	−0.89 to 0.57

CI = confidence interval; LS = least squares; SE = standard error.
95% CI for treatment comparison was based on an analysis of covariance model with treatment group as factor and time-matched baseline intraocular pressure as covariate at each time point. Analysis performed on the intention-to-treat analysis set. If a patient was taking additional intraocular pressure-lowering medication at a specific visit after day 5 (or the washout window for the medication covered the day of the visit), then the patient was considered on additional intraocular pressure-lowering medication for that visit alone. For patients without intercurrent events, multiple imputation technique was used to impute the missing data; for patients with intercurrent events, worse-half multiple imputation technique was used for imputation.

treatment, and none were considered related to study treatment in the timolol group.

Overall, most patients with ocular AEs in the study eye experienced mild AEs. Severe ocular AEs were reported in 4 patients in each of the FE and SE implant groups. Single severe AEs were reported for 3 patients in the FE implant group (device dislocation, ocular hyperemia, and IOP increased). One patient in the FE implant group and 4 patients in the SE implant group reported multiple severe AEs. Specifically, 1 patient in the FE implant group experienced severe AEs of reduced visual acuity and increased IOP (all related to study treatment). In the SE implant group, severe AEs of foreign body sensation in eye, photophobia, and increased lacrimation (all related to study treatment) were reported in 1 patient; severe AEs of endophthalmitis, iritis, decreased visual acuity, and increased IOP (all related to study treatment) were reported in 1 patient; severe AEs of conjunctival hyperemia and photophobia (both related to study treatment) were reported in 1 patient; and severe AEs of intermittent iritis, uveitis, reduced visual acuity, increased IOP, corneal edema, cataract, and posterior capsular opacification (all related to study treatment except posterior capsular opacification) were reported in 1 patient. No patient in the timolol group experienced a severe ocular AE.

Implant dislodgement (device dislocation) was reported in single patients in both the FE and SE implant groups, resulting in explantation in the patient with the FE implant during the 3-month evaluation period. Two additional patients (1 in each of the implant groups) at 1 site also underwent explantation because of treatment-related AEs of uveitis.

The vast majority (> 90%) of sites used topical anesthesia, including topical ocular drops, intracameral lidocaine, or both, for the administration procedure. A total of 3 of the 44 sites used a retrobulbar or peribulbar block because this was the standard procedure for all surgical cases.

Little difference was found in change from baseline in central corneal endothelial cell counts between the implant groups and timolol group at month 3. The mean percent change was −2.69 ± 5.78% in the FE implant group (n = 26), −1.93 ± 4.37% in the SE implant group (n = 20), and −0.96 ± 5.04% in the timolol group (n = 20), with no study eye exceeding the predefined threshold of a ≥ 30% decrease from baseline. Mean best spectacle-corrected visual acuity values in the implant and timolol groups were within 1 letter from baseline at all visits (Table S9, available at www.aaojournal.org).

The vast majority (≥ 94%) of study eyes in both implant groups showed normal to mild (grade 0, 0.5, or 1 on a 5-point scale of 0 indicating normal to 3 indicating severe) conjunctival hyperemia at all visits, with only 2 reports of severe hyperemia observed (in the FE implant group at day 10 and week 4) during the 3-month period (Table S10, available at www.aaojournal.org). Mean conjunctival hyperemia grade by visit is shown in Figure S5 (available at www.aaojournal.org).

Discussion

This pivotal clinical trial demonstrated that both the FE and SE travoprost intraocular implants provide clinically relevant IOP reductions from baseline over 3 months of treatment after a single administration. Intraocular pressure reductions from an unmedicated baseline (mean diurnal IOP of 24 mmHg) across the 6 time points through month 3 ranged from 6.6 to 8.4 mmHg in the FE implant group and from 6.6 to 8.5 mmHg in the SE implant group. These reductions, ranging from 6.5 to 7.7 mmHg, were similar to

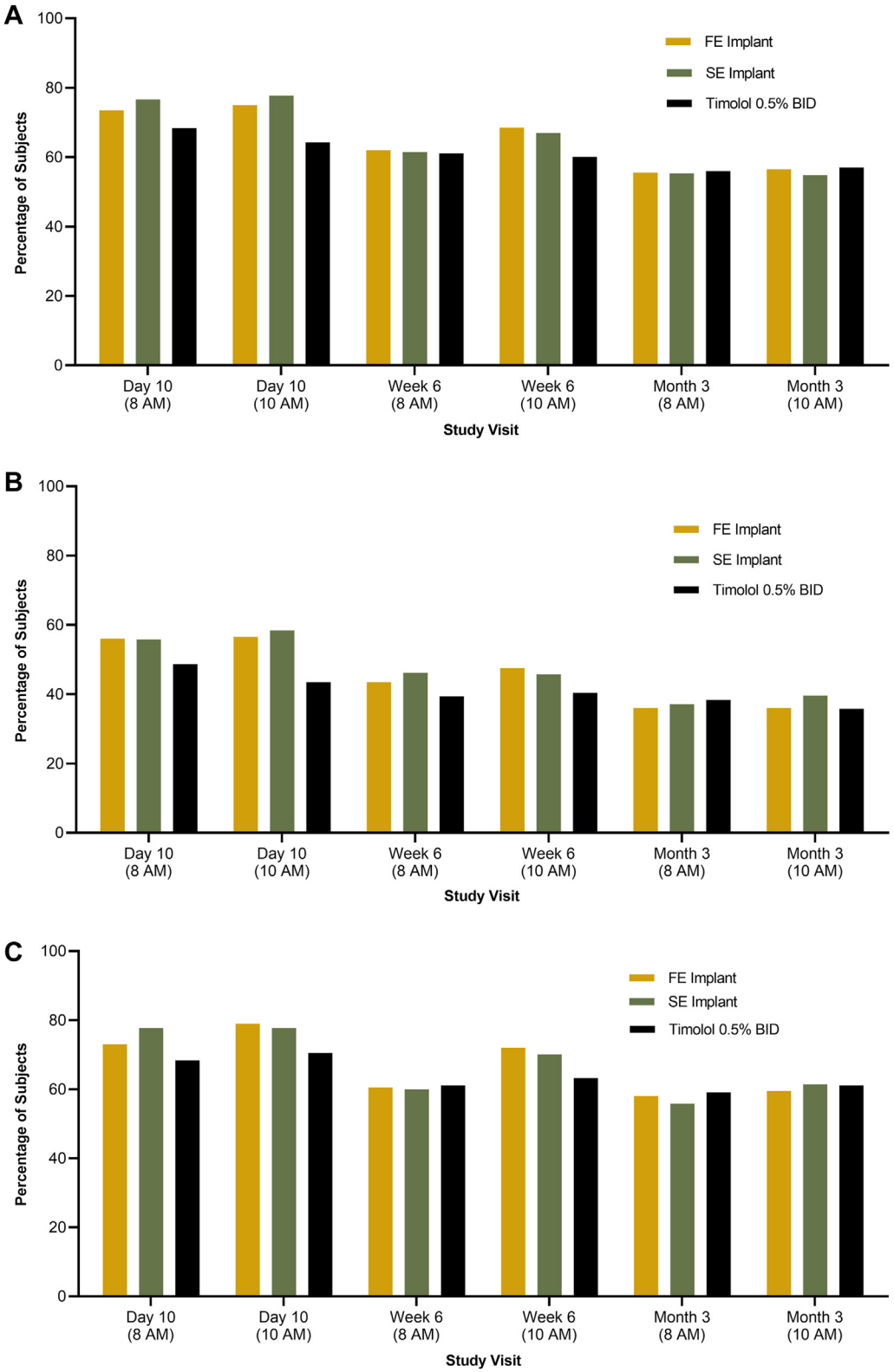

Figure 3. Bar graphs showing the percentage of patients achieving (**A**) an intraocular pressure (IOP) reduction from baseline of 25% or more, (**B**) an IOP reduction from baseline of 8 mmHg or more, and (**C**) an IOP reduction of 18 mmHg or less. BID = twice daily; FE = fast-eluting; SE = slow-eluting.

Table 8. Most Common Adverse Events in the Study Eye (≥ 3% in Any Treatment Group)

Medical Dictionary for Regulatory Activities Preferred Term*	Fast-Eluting Implant (n = 200)	Slow-Eluting Implant (n = 195)	Timolol (n = 194)
Patients with any adverse events in the study eye	43 (21.5)	53 (27.2)	21 (10.8)
Intraocular pressure increased	7 (3.5)	5 (2.6)	4 (2.1)
Iritis	1 (0.5)	10 (5.1)	0
Ocular hyperemia	6 (3.0)	5 (2.6)	0
Visual acuity reduced	2 (1.0)	8 (4.1)	1 (0.5)

Analysis performed on the safety analysis set.
*Presented in alphabetical order.

those observed with twice-daily timolol maleate ophthalmic solution 0.5%.

The IOP-lowering efficacy of the FE and SE implants was statistically and clinically noninferior to timolol. The upper limit of the 95% CI of the difference between the implant groups and the timolol group was < 1.5 mmHg and also < 1 mmHg at all 6 time points (8 AM and 10 AM at day 10, week 6, and month 3). The robustness of the primary efficacy outcomes was confirmed in sensitivity analyses using an ANCOVA with various methods to impute missing data on the ITT and per-protocol analysis sets, as well as the trimmed mean permutation test method.

The criteria for noninferiority used in the current trial generally are consistent with the noninferiority margin used in other registration trials of glaucoma medications. Because the travoprost intraocular implant continuously elutes travoprost, the IOP assessments at 8 AM and 10 AM were chosen to capture the trough and peak IOP effects, respectively, of the timolol control treatment. Comparisons of topical travoprost and timolol have required IOP assessments at 8 AM, 10 AM, and 4 PM to capture the trough and peak IOP effects of both topical medications.[16,17] To address this difference in IOP measurement time points, ad hoc sensitivity analyses of the change from baseline in diurnal IOP were conducted using the 9 time points (i.e., 8 AM, 10 AM, and 4 PM time points at day 10, week 6, and month 3). The results of these analyses also demonstrated that the implants were statistically and clinically noninferior to timolol; the upper limit of the 95% CI of the difference between both implant groups and the timolol group was < 1.5 mmHg and also < 1 mmHg for all 9 time points.

Despite a lower mean diurnal IOP at baseline, the IOP reductions in the FE and SE travoprost intraocular implant groups are similar to those reported with travoprost ophthalmic solution 0.004% in registration trials for the product (7.0−8.0 mmHg across the 8 AM and 10 AM time points at week 2, month 1.5, and month 3 from an unmedicated baseline mean diurnal IOP of 26 mmHg).[16,17] Furthermore, in the current study, IOP reductions from baseline with timolol 0.5% twice daily ranged from 6.5 to 7.7 mmHg compared with 5.8 to 7.1 mmHg elicited by timolol 0.5% twice daily across these same 6 time points in the travoprost registration trials.[16,17]

Secondary efficacy outcomes were consistent with the primary outcomes. Low percentages of patients required additional IOP-lowering medications at month 3: 5.1% and 4.2% in the FE and SE implant groups, respectively, versus 7.0% in the timolol group, although approximately 22% of patients were receiving ≥ 2 classes of IOP-lowering medication at screening. In addition, clinically relevant percentages of patients achieved an IOP reduction of at least 25%, an IOP reduction from baseline of at least 8 mmHg, and a target IOP of ≤ 18 mmHg at most time points through month 3.

The overall safety of the travoprost intraocular implants was favorable. Although AEs in the study eye were more common overall in the implant groups than in the topical timolol group, most of these events were of mild or moderate severity and did not compromise vision. Device dislocation was reported in single patients in each of the implant groups (i.e., an incidence of 0.5% per group), and endophthalmitis was reported in a single patient in the SE implant group. Endophthalmitis is a risk for all other intraocular surgical procedures and injections, and its occurrence in this study highlights the importance of using proper aseptic technique on administration and appropriate monitoring to ensure prompt treatment.

Central corneal endothelial cell count remained relatively stable with a mean percent change of −2.7% and −1.9% in the FE and SE implant groups, respectively, compared with −1.0% in the timolol group. No patient met the predefined threshold of a loss of ≥ 30%. The ≥ 30% threshold may be a limitation of our analyses; however, this threshold was agreed to with the United States FDA prospectively and was confirmed via extensive dialogue with the independent, masked, corneal endothelial cell reading center used for this trial. Another limitation of our analyses may be the small subset of patients (only 10% to 13% of patients in each of the treatment groups) in which endothelial cell counts were measured. Mean conjunctival hyperemia scores were higher in the implant groups than the timolol group at all time points; however, the mean score was < 0.5 at all time points, indicating that most patients experienced normal or trace hyperemia.

The limitation of this analysis is its relatively short duration, which does not allow for evaluation of the long-term safety or efficacy of the travoprost intraocular implant. However, a primary efficacy end point with IOP assessment at multiple time points over a 3-month period is required for United States FDA approval of IOP-lowering medications. Furthermore, the trial is ongoing to obtain 3-year efficacy and safety data. Another limitation is the use

of timolol rather than a topical PGA such as travoprost as the comparator. However, timolol has been used historically as an active comparator in trials of new IOP-lowering therapies because of its well-established efficacy and safety profile and continues to be used as an active comparator for registration trials (ClinicalTrial.gov identifier, NCT03691662 and NCT03691649), despite PGAs now being the most prescribed topical medications for lowering IOP. A fellow-eye timolol-controlled comparison also may have been a valid comparison; however, various studies have shown that topical timolol has an IOP-lowering effect in the contralateral eye.[19,20] The fellow eye was treated with timolol-containing eye drops in 25.0% of patients receiving FE implants and 21.3% of patients receiving SE implants in our study; however, a sensitivity analysis demonstrated that the noninferiority criteria for the FE and SE implant groups to the timolol group were still met after removing these patients, thus confirming that the IOP-lowering effects in the implant eyes were not dependent on a crossover effect from the fellow eyes dosed with timolol. Another limitation is that surgeons administering the implant and individuals performing assessments of the anterior segment clearly were not masked to treatment. However, to mitigate this potential source of bias, IOP was assessed using a 2-examiner (operator and masked reader) technique. Also, to mask patients and other study personnel, a sham procedure was used for masking in the timolol group, and an artificial tear solution was used as the placebo solution for masking in the implant groups.

Despite these limitations, this study indicated that both models of the travoprost intraocular implant provide clinically relevant, sustained IOP reductions over the 3-month period after a single administration that are noninferior to those produced by twice-daily administered timolol ophthalmic solution 0.5%. The overall safety profile was favorable, and the travoprost intraocular implants were well tolerated, with the ongoing evaluation designed to provide further evidence of the implants' safety through 3 years after administration. In summary, the travoprost intraocular implant demonstrated robust IOP reduction that was noninferior to timolol over a 3-month primary efficacy evaluation period and provided an alternative to topical IOP-lowering medication.

Footnotes and Disclosures

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*A list of members of the GC-010 Travoprost Intraocular Implant Investigators appear in the Appendix (available at aaojournal.org).

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The author(s) have made the following disclosure(s):

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A.C.K.: Employee and Equity owner − Glaukos

D.W.U.: Employee and Equity owner − Glaukos

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T.N.: Employee and Equity owner − Glaukos

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HUMAN SUBJECTS: Human subjects were included in this study. Institutional review board/independent ethics committee approval (Western Institutional Review Board for 43 sites, Wills Eye Hospital Institutional Review Board for 1 site, and St. Cabrini Medical Center-Asian Eye Institute

Ethics Review Committee for 1 site) was obtained for the trial and subjects provided written informed consent prior to undertaking any study-related procedures. The clinical trial was registered at ClinicalTrials.gov (NCT 03519386) and was conducted in accordance with good clinical practices and the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Doan, Stephens, Katz

Analysis and interpretation: Sarkisian, Ang, Lee, Berdahl, Heersink, Burden, Doan, Stephens, Kothe, Usner, Katz, Navratil

Data collection: Sarkisian, Ang, Lee, Berdahl, Heersink, Burden

Obtained funding: N/A

Overall responsibility: Sarkisian, Ang, Lee, Berdahl, Heersink, Burden, Doan, Stephens, Kothe, Usner, Katz, Navratil

Abbreviations and Acronyms:
ANCOVA = analysis of covariance; **CI** = confidence interval; **dB** = decibels; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FDA** = Food and Drug Administration; **FE** = fast-eluting; **ICE** = intercurrent event; **IOP** = intraocular pressure; **ITT** = intention-to-treat; **LS** = least squares; **MCMC** = Monte Carlo Markov chain; **MI** = multiple imputation; **PGA** = prostaglandin analog; **SD** = standard deviation; **SE** = slow-eluting; **TEAE** = treatment-emergent adverse event; **USP** = United States Pharmacopeia.

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