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Phase 3, Randomized, 20-Month Study of Bimatoprost Implant in Open-Angle Glaucoma and Ocular Hypertension (ARTEMIS 1)

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Purpose: To evaluate the intraocular pressure (IOP)-lowering efficacy and safety of 10- and 15-μg bimatoprost implant in subjects with open-angle glaucoma (OAG) and ocular hypertension (OHT) after initial and repeated administrations.

Design: Randomized, 20-month, multicenter, subject- and efficacy evaluator-masked, parallel-group, phase 3 clinical study.

Participants: Adults with OAG or OHT in each eye, open iridocorneal angle inferiorly in the study eye, and study eye baseline IOP (hour 0; 8 AM) of 22–32 mmHg after washout.

Methods: Study eyes received bimatoprost implant 10 μg (n = 198) or 15 μg (n = 198) on day 1 with readministration at weeks 16 and 32, or twice-daily topical timolol maleate 0.5% (n = 198). Intraocular pressure was measured at hours 0 and 2 at each visit.

Main Outcome Measures: Primary end points were IOP and change from baseline IOP through week 12. Safety measures included treatment-emergent adverse events (TEAEs) and corneal endothelial cell density (CECD).

Results: Both dose strengths of bimatoprost implant were noninferior to timolol in IOP lowering after each administration. Mean diurnal IOP was 24.0, 24.2, and 23.9 mmHg at baseline and from 16.5–17.2, 16.5–17.0, and 17.1–17.5 mmHg through week 12 in the 10-μg implant, 15-μg implant, and timolol groups, respectively. The incidence of corneal and inflammatory TEAEs of interest (e.g., corneal endothelial cell loss, iritis) was higher with bimatoprost implant than timolol and highest with the 15-μg dose strength. Incidence of corneal TEAEs increased after repeated treatment; with 3 administrations at fixed 16-week intervals, incidence of ≥20% CECD loss was 10.2% (10-μg implant) and 21.8% (15-μg implant). Mean best-corrected visual acuity (BCVA) was stable; 3 implant-treated subjects with corneal TEAEs had >2-line BCVA loss at their last visit.

Conclusions: Both dose strengths of bimatoprost implant met the primary end point of noninferiority to timolol through week 12. One year after 3 administrations, IOP was controlled in most subjects without additional treatment. The risk-benefit assessment favored the 10-μg implant over the 15-μg implant. Ongoing studies are evaluating other administration regimens to reduce the potential for CECD loss. The bimatoprost implant has potential to improve adherence and reduce treatment burden in glaucoma. *Ophthalmology 2020;127:1627-1641 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Open-angle glaucoma (OAG) is a vision-threatening, chronic, irreversible disease that requires intraocular pressure (IOP)-lowering treatment to slow or prevent progression.[1,2] Early management and adherence to treatment are important because quality of life decreases, and the economic costs of glaucoma increase, as the disease advances.[3-6] Topical ophthalmic medications are typically used as first-line treatment in OAG, and the prostaglandin analog (PGA) class of topical IOP-lowering medications is often used as initial treatment because the PGA medications are the most efficacious in lowering IOP, well tolerated, and systemically safe.[7,8] Numerous studies have demonstrated the IOP-lowering efficacy of topical PGAs such as bimatoprost, latanoprost, tafluprost, and travoprost in clinical trials and real-world clinical settings.[7,9,10] However, nonadherence to treatment is common in glaucoma.[11,12] A study using pharmacy claims data showed that patients filled prescriptions for topical PGAs and had medication

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available for dosing only 37% of the days in a year.[12] Importantly, treatment nonadherence is associated with worse visual outcomes.[13,14] Longitudinal assessment of patients treated for an average of 7.3 years with topical IOP-lowering medication in the Collaborative Initial Glaucoma Treatment Study demonstrated a statistically and clinically significant association between medication nonadherence and glaucomatous vision loss.[14] Barriers to adherence to topical IOP-lowering medications include patient forgetfulness, side effects, and difficulty in instilling eye drops.[11,13,15-17] Therefore, there is a need for well-tolerated treatments that deliver IOP-lowering medication over extended periods of time without need for daily eye drops.

Bimatoprost implant (Durysta; Allergan plc, Dublin, Ireland) is an intracameral, biodegradable implant (Fig 1) designed to release bimatoprost for 3−4 months. The rod-shaped implant is an ophthalmic drug delivery system (Allergan plc), which consists of biodegradable polymers (similar to those in biodegradable sutures) and has been used as a delivery system for dexamethasone in the treatment of other ophthalmic diseases since 2009.[18] After administration with a single-use, 28-gauge applicator, the implant provides nonpulsatile, continuous release of bimatoprost,[19] and the polymer matrix is biodegraded through hydrolysis and metabolism to carbon dioxide and water.[18,20]

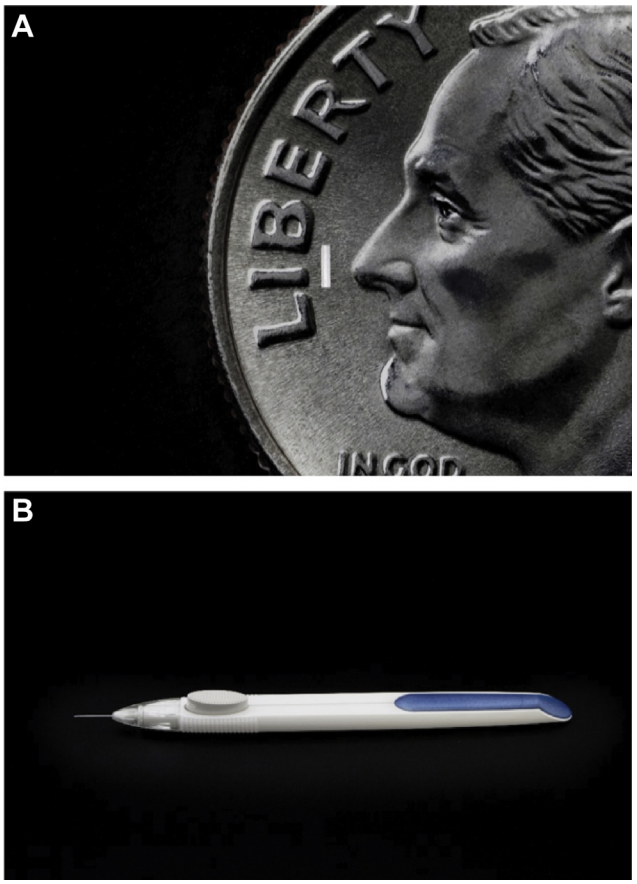

Figure 1. Bimatoprost implant drug delivery system. **A,** Images of an implant (10-μg dose strength) and a dime are superimposed for size comparison. The implant is similar in size to the "i" in Liberty on the dime. A single-use, 28-gauge applicator **(B)** is used to administer the implant intracamerally.

In a nonclinical study using normotensive dogs, administration of bimatoprost implant was shown to enhance delivery of bimatoprost to the iris−ciliary body (a target tissue for IOP lowering) and achieve drug concentrations 4400-fold higher than those achieved with bimatoprost 0.03% eye drops.[21] Drug distribution to ocular surface and periocular tissues typically associated with PGA-related side effects (i.e., bulbar conjunctiva, eyelid margins, and periorbital fat) was decreased or below detectable levels with bimatoprost implant compared with topical bimatoprost 0.03%.[21] Drug delivery with bimatoprost implant placed intracamerally thus has the potential to minimize periorbital and ocular surface adverse effects associated with topical PGA administration. Furthermore, drug release from bimatoprost implant is continuous, as shown by the in vitro drug release profile from the implant (Fig S1, available at www.aaojournal.org). This continuous drug release from the implant would provide more consistent drug exposure to target tissues, whereas topical PGA administration delivers peak and trough drug levels to tissues,[22] and therapeutic concentrations may not be maintained.

A 24-month, paired-eye, phase 1/2 clinical study evaluated the safety and efficacy of 4 dose strengths of bimatoprost implant (6, 10, 15, and 20 μg) in OAG.[19] In an interim published report at 6 months, the average IOP change from baseline in study eyes over 16 weeks after a single implant administration was similar to that observed in fellow eyes treated with once-daily bimatoprost 0.03% eye drops.[19] Moreover, the safety profile of bimatoprost implant was favorable; no serious ocular adverse events were reported in study eyes, and no implant had to be removed.[19] Results of the completed study showed a frequent extended duration of IOP lowering with the implant: 68%, 40%, and 28% of study eyes that received bimatoprost implant on day 1 were controlled without any additional treatment up to months 6, 12, and 24, respectively.[23]

The present phase 3 study evaluated the efficacy and safety of 2 dose strengths of bimatoprost implant (10 and 15 μg) after initial and repeated administration compared with twice daily (BID) timolol maleate 0.5% eye drops in research subjects with OAG or ocular hypertension (OHT). The clinical hypothesis was that at least 1 dose strength of bimatoprost implant would have an acceptable safety profile and would be noninferior to timolol eye drops in lowering IOP after single and repeat administration.

Methods

Study Design

A randomized, multicenter, subject- and efficacy evaluator-masked, parallel-group, active-controlled, 20-month (52-week active treatment period with 8 months extended follow-up), phase 3 clinical trial (ARTEMIS 1) evaluated the efficacy and safety of bimatoprost implant in comparison with topical timolol

for lowering IOP in subjects with OAG or OHT. The study was conducted at 108 sites in 14 countries: Australia, Austria, Belgium, Brazil, Denmark, Hong Kong, Hungary, Israel, Peru, Philippines, Poland, Spain, Taiwan, and the United States. The study adhered to the tenets of the Declaration of Helsinki and was conducted in conformance with the International Conference on Harmonization E6 guideline for Good Clinical Practice or the laws and regulations of the country in which the research was conducted—whichever afforded greater protection to the individual. Institutional Review Board/Ethics Committee approval was obtained at each site. All subjects provided written informed consent. The study is registered with the identifier NCT02247804 at ClinicalTrials.gov.

Participants

Adults ≥18 years of age diagnosed with OAG or OHT in each eye, with both eyes requiring IOP-lowering treatment, were enrolled. Key inclusion criteria included baseline IOP in the study eye after washout within the range of 22−32 mmHg at hour 0 (8 AM ± 1 hour) and 19−32 mmHg at hour 2 (2 hours after hour 0; expected peak effect of the comparator timolol); study eye inferior iridocorneal angle Shaffer grade of ≥3 on gonioscopy and peripheral anterior chamber depth of ≥1/2 corneal thickness by Van Herick estimation; and central corneal endothelial cell density (CECD) by specular microscopy of ≥1800 cells/mm^2 in at least 1 eye by automated analysis at screening, with central CECD confirmed as qualified by the central reading center (Doheny Image Reading Center, Los Angeles, CA) in both eyes by baseline.

Key exclusion criteria included history of anatomically narrow angle that resulted in evidence of angle changes, or history of closed-angle glaucoma in either eye; subject nonresponsive to topical ophthalmic beta-blockers and/or PGAs; peripheral anterior synechiae in the inferior iridocorneal angle on gonioscopic examination at screening in either eye; history or evidence of complicated cataract surgery in the study eye; and any contraindication to beta-blocker therapy. A complete listing of all eligibility criteria for the study is provided in Table S1 (available at www.aaojournal.org).

If both eyes were eligible to be the study eye, the eye with the higher IOP at baseline (hour 0) was selected as the study eye. If both eyes had the same IOP, the right eye was selected as the study eye.

Visit Schedule

Study visits included screening and baseline visits; visits during 3 treatment cycles at day 1 (administration 1) and weeks 2, 6, 12, 15, 16 (administration 2), 18, 22, 28, 31, 32 (administration 3), 34, 38, 44, 48, and 52; and visits during extended safety follow-up at months 14, 16, 18, and 20. In addition, study safety visits were scheduled 1 day after each administration visit, and 6 phone calls were made for safety assessment at 3 and 7 days after each administration visit.

Subjects were to be followed through month 20 or for at least 12 months after their last bimatoprost implant or sham administration. Subjects who received <3 administrations were expected to remain in the study for 12 months after the last administration, at which point they could complete and exit the study if there were no safety concerns.

Randomization, Intervention, and Masking

Subjects using IOP-lowering medication at the time of screening underwent washout before baseline for up to 42 days, with a minimum washout period of 4 days for parasympathomimetics and carbonic anhydrase inhibitors, 14 days for sympathomimetics and alpha-adrenergic agonists, and 28 days for beta-adrenergic antagonists and PGAs.

On day 1, subjects were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: 10-μg bimatoprost implant, 15-μg bimatoprost implant, and timolol. The randomization was based on a computer-generated randomization scheme provided by the sponsor and was stratified by baseline study eye hour 0 IOP of ≤25 or >25 mmHg. An automated interactive voice response system/interactive web response system was used to manage the randomization and treatment assignment, and to provide sites with the specific medication kit number(s) for each randomized subject.

Study eyes in the bimatoprost implant groups received implant on administration day visits (day 1, week 16, and week 32) and vehicle eye drops BID for masking (Fig S2, available at www.aaojournal.org). Study eyes in the timolol group received topical timolol maleate 0.5% (timolol) BID and a sham procedure on administration day visits for masking. All fellow eyes were treated with timolol BID and received a sham procedure on administration visit days. Adherence to the eye drops was not assessed.

The ophthalmologists who performed the administrations were required to be active ophthalmic surgeons, and they were trained on the administration technique by qualified study personnel in hands-on training sessions at investigator meetings. The ophthalmologists were observed during training to ensure competency before being approved by the sponsor to perform the procedure. At the discretion of the investigator, the bimatoprost implant and sham administrations could be performed at an ambulatory surgical center or in the office setting (e.g., in a procedure room with an operating microscope) with the subject supine. On administration visit days, eyes were prepared for intraocular injection using standard practice for an intraocular procedure, with topical antibiotic (gatifloxacin, moxifloxacin, or another broad-spectrum ophthalmic antibiotic drop) and topical anesthetic applied to each eye before the procedure, irrigation of the eyes and conjunctival fornices with povidone-iodine 5% ophthalmic solution, and use of a sterile surgical drape and lid speculum. The bimatoprost implant was administered intracamerally (Video 1, available at www.aaojournal.org) with a single-use, prefilled applicator system. With a delicate-toothed tissue forceps or a cotton-tipped applicator used to stabilize the eye, the applicator needle was inserted through the peripheral clear cornea, parallel to the iris plane and avoiding the pupil, with the needle bevel visible. The actuator button was then pressed to release the implant, the needle was removed from the anterior chamber, and tamponade was applied to the needle track. After ensuring no aqueous leakage from the needle track, the lid speculum and sterile drape were removed, and a broad-spectrum topical antibiotic was applied and used for the next 3 days. The procedure for sham administrations was the same, but instead of an intraocular injection, a needleless applicator was used to touch the cornea. Sterile technique was used throughout the administration procedures.

Timolol and vehicle eye drops were provided in identically appearing masked bottles labeled for eye of administration ("Left" or "Right") and were self-administered by the subjects at 8 AM (±1 hour) and 8 PM (±1 hour) daily, beginning on the evening of the first administration visit (day 1). Subjects were asked not to administer their drops on the morning of a study visit; instead, the drops were administered at the study site immediately after the hour 0 IOP assessment.

The second and third administration of the bimatoprost implant or sham procedure could be withheld in the event of a safety concern, including clinically significant endothelial cell loss. In each treatment group, use of nonstudy IOP-lowering medication in

either eye was allowed during the first 52 weeks (after confirmation of IOP at a subsequent visit) if determined by the investigator to be required for safety reasons due to inadequate IOP control, and after the week 52 visit if, in the judgment of the investigator, the IOP was not adequately controlled at 2 consecutive visits.

Subjects and the site personnel who collected efficacy data were masked to the treatment and study eye assignment. The investigators who performed bimatoprost implant/sham administration and designated unmasked site staff (e.g., those assisting during administration) were masked to the bimatoprost implant dose strength that the subject received. In addition, to maintain masking, any subject who used nonstudy IOP-lowering treatment in 1 eye continued to use the study-provided eye drops in both eyes, and if the eye that received the nonstudy IOP-lowering treatment was a study eye assigned to bimatoprost implant treatment, the eye received sham administrations on any subsequent administration days. If nonstudy IOP-lowering treatment was used in both eyes, the subject discontinued all use of study-provided eye drops and received no further bimatoprost implant or sham administration in either eye.

Assessments and Outcome Measures

At all visits except administration visits, IOP was measured in each eye at hour 0 and hour 2 with Goldmann applanation tonometry using a 2-person, masked reading method.[24] Two measurements were taken for each eye, and if the measurements differed by >1 mmHg, a third measurement was taken. The mean of 2 measurements or the median of 3 measurements was used for analysis.

The key efficacy outcome measures were IOP and change in IOP from baseline. The primary efficacy end point used for application for drug approval by the US Food and Drug Administration was the study eye IOP at each hour (hours 0 and 2) at weeks 2, 6, and 12. A secondary primary end point, used for applications for drug approval by regulatory agencies in other countries, was the hour-matched IOP change from baseline in the study eye at each hour (hour 0 and hour 2) at week 12.

Safety measures included adverse events, CECD evaluated with specular microscopy, corneal thickness with ultrasound (contact) pachymetry, biomicroscopy including gonioscopy with bimatoprost implant assessment, best-corrected visual acuity (BCVA), and dilated fundus examinations. Treatment-emergent adverse events (TEAEs) were defined as adverse events with onset or increased severity, or that became serious, on or after the first study treatment date. Treatment-emergent adverse events of special interest included corneal TEAEs of interest (corneal endothelial cell loss, edema, opacity, touch, disorder, or thickening), as well as anterior segment and vitreous inflammatory TEAEs of interest (iritis, anterior chamber cell, iris adhesions, anterior chamber flare, keratitis, uveitis, anterior chamber inflammation, iridocyclitis, keratic precipitates, and vitreal cells).

Statistical Analysis

Statistical analyses were performed with SAS version 9.3 or 9.4 software (SAS Institute Inc, Cary, NC). The analyses reported used the final database lock from the completed study. Previous planned interim analyses used database locks at weeks 12 and 52, when all subjects who had not discontinued from the study had completed the week 12 and week 52 visits, respectively. All statistical tests were 2-sided with an alpha level of 0.05. The primary analyses of IOP used observed values in the intent-to-treat population of all randomized subjects. To avoid confounding of the efficacy data, IOP measurements taken after initiating use of a nonstudy IOP-lowering medication or procedure in an eye were excluded from analysis.

Analysis of the primary end point used a mixed-effect model for repeated measures (MMRM) model including IOP as the response variable; fixed effects of treatment, time point (hours 0 and 2 at weeks 2, 6, and 12), treatment-by-time point interaction, and baseline IOP stratification ($\leq$25 and >25 mmHg); hour-matched baseline IOP as a covariate; and the time point-by-baseline hour-matched IOP interaction. An unstructured covariance matrix was used for repeated measures, and any IOP measurements taken after initiation of use of nonstudy IOP-lowering medication in an eye were treated as missing. The difference between each bimatoprost implant dose strength and timolol (bimatoprost implant group minus timolol group) and the corresponding 2-sided 95% confidence interval (CI) for each time point were calculated on the basis of the MMRM model. Noninferiority of bimatoprost implant to timolol was established if the upper limit of the 95% CI was $\leq$1.5 mmHg for all time points. If noninferiority to timolol was established, the bimatoprost implant dose strength was to be declared clinically noninferior to timolol if the upper limit of the 95% CI was $\leq$1.0 mmHg for $\geq$3 time points. A gatekeeping procedure with a prespecified testing sequence was used to control the overall type I error rate at the 0.05 level. For each time point, noninferiority of 15-μg bimatoprost implant to timolol was tested first, and if noninferiority was established, noninferiority of 10-μg bimatoprost implant to timolol was tested. Superiority tests were performed after noninferiority was established, with the bimatoprost implant dose strength declared to be superior to timolol at a time point if the upper limit of the 95% CI was <0 mmHg. For clinical significance, the upper limit of the 95% CI had to be <0 mmHg at all 6 time points.

Analysis of IOP change from baseline used a similar MMRM approach with IOP hour-matched change from baseline as the response variable, and noninferiority was to be declared if the 95% CI of the between-group difference was within a 1.5-mmHg noninferiority margin at both hours 0 and 2 at week 12. For subjects who received repeat administration in the study eye, IOP and IOP change from the study baseline were analyzed at hours 0 and 2 at 2, 6, and 12 weeks after the second and third administration using similar MMRM models.

Intraocular pressure, diurnal IOP (average of the hour 0 and hour 2 measurements), change from baseline IOP, and number of subjects who had used additional treatment (i.e., a nonstudy IOP-lowering medication or procedure) in the study eye were summarized with descriptive statistics. Kaplan–Meier survival analysis was used to estimate time to initial use of additional treatment in the study eye after the last administration before use of additional treatment, and for subjects who received 3 administrations in the study eye, time to initial use of additional treatment after the third administration. In each analysis, if a subject did not use any additional IOP-lowering treatment in the study eye during the study period, the subject's study exit date (or last visit date, if the exit date was unavailable) was used as the censoring date.

Safety parameters were evaluated using the safety population of all subjects who received a study treatment. Analyses were performed by treatment group for study eyes, based on the first treatment actually received in the eye, and were pooled for fellow eyes. In analyses by administration cycle, rates of TEAEs were also evaluated after each administration, for subjects who received the administration, and during the extended safety follow-up period, for subjects who received 3 administrations.

Enrollment of approximately 600 subjects (200 per each treatment group) was planned to provide 95% power to show noninferiority of 15-μg bimatoprost implant to timolol and 81%

power to show noninferiority of 10-μg bimatoprost implant to timolol, based on a 2-sided t test with $\alpha = 0.05$ at each time point, assuming a study discontinuation rate of 10% within the primary efficacy period (12 weeks), and using estimates of IOP variability and between-group differences from a previous study.[19]

Results

A total of 594 subjects were enrolled from December 2014 to September 2017, and the study was completed in July 2019. Subjects were randomized to the 10-μg bimatoprost implant (n = 198), 15-μg bimatoprost implant (n = 198), and BID timolol (n = 198) treatment groups. Baseline demographics and study eye characteristics were generally well balanced among treatment groups (Table 1). The mean age of the study population was 62.5 years, and 51.5% of the subjects were male. Subjects were predominantly white (63.1%), black (13.8%), or Hispanic (12.6%). Most of the study eyes (78.1%) were diagnosed with primary OAG (Table 1). Mean IOP in study eyes was similar among the treatment groups at both hour 0 and hour 2 (Table 1).

Figure S3 (available at www.aaojournal.org) shows subject flow through the study. Study completion rates were 90.4%, 79.3%, and 86.9% in the 10-μg bimatoprost implant, 15-μg bimatoprost implant, and timolol groups, respectively. The most common reasons for not completing the study (i.e., early exits) were adverse events and personal reasons (Fig S3, available at www.aaojournal.org). Treatment-emergent adverse events most often leading to early exit from the bimatoprost implant treatment groups included corneal endothelial cell loss and corneal edema.

Study drug exposure was evaluated in the safety population of all treated subjects. In the 10-μg bimatoprost implant group, 174 subjects (88.3%) received 3 implant administrations, 14 subjects (7.1%) received 2 implant administrations, and 9 subjects (4.6%) received 1 implant administration. In the 15-μg bimatoprost implant group, 151 subjects (78.2%) received 3 implant administrations, 18 subjects (9.3%) received 2 implant administrations, and 24 subjects (12.4%) received 1 implant administration. The most common reasons for not receiving all 3 implant administrations were occurrence of a TEAE and use of nonstudy IOP-lowering treatment in the study eye.

Gonioscopic examinations showed that the implants typically resided in the inferior iridocorneal angle. The implants were often observed to initially swell as they biodegraded. At week 12 after the first administration, visible implant on gonioscopic examination was reported in the study eye of 96.3% (364/378) of bimatoprost implant−treated subjects, and among subjects with implant size assessments, the implant was estimated to be 101%−150% of initial size for 25.5% (27/106) and 38.5% (40/104) of subjects and ≥151% of initial size for 14.2% (15/106) and 7.7% (8/104) of subjects in the 10-μg and 15-μg bimatoprost implant groups, respectively. At the end of the active treatment study period (week 52), visible implant on gonioscopic examination was reported in the study eye of 96.3% (313/325) of bimatoprost implant−treated subjects. At this time point, among subjects in both the 10-μg and 15-μg bimatoprost implant groups who had implant size assessments, the first implant was most commonly not visible or estimated to be 0%−25% of initial size, the second implant was most commonly estimated to be 26%−50% of initial size, and the third implant was most commonly estimated to be 51%−75% of initial size. In assessments at month 20, 1 or more visible implants on gonioscopic examination were reported in the study eye of 85.5% (271/317) of bimatoprost implant−treated subjects; the implants were typically estimated to be 0%−25% of initial size.

Primary End Points: Intraocular Pressure Lowering through 12 Weeks after Administration

Through week 12, 98.5% (195/198), 95.5% (189/198), and 98.0% (194/198) of subjects in the 10-μg bimatoprost implant, 15-μg bimatoprost implant, and timolol groups, respectively, remained in the study and had not received nonstudy IOP-lowering treatment in the study eye. At all time points in the primary efficacy period (hours 0 and 2 at weeks 2, 6, and 12), mean IOP in study eyes was consistently lower and mean change in IOP from baseline was consistently larger in the bimatoprost implant groups than in the timolol group (Figs 2A and 3A). Both dose strengths of bimatoprost implant met the a priori criteria for statistical and clinical noninferiority to timolol in IOP and change in IOP from baseline (Figs 2B and 3B). In the analyses of both mean IOP and mean change in IOP from baseline, the upper limit of the 95% CI of the difference between bimatoprost implant and timolol was <1.0 mmHg at all time points for both dose strengths and was <0 mmHg (indicating superiority of bimatoprost implant to timolol) at 4 of 6 time points for the 10-μg dose strength and at 3 of 6 time points for the 15-μg dose strength (Figs 2B and 3B).

The mean (standard deviation) diurnal IOP at baseline was 24.0 (2.7), 24.2 (2.8), and 23.9 (2.6) mmHg for study eyes in the 10-μg bimatoprost implant, 15-μg bimatoprost implant, and timolol groups, respectively. The mean (standard deviation) diurnal IOP for study eyes at weeks 2, 6, and 12, respectively, was 16.6 (3.1), 16.5 (3.0), and 17.2 (3.6) mmHg in the 10-μg bimatoprost implant group, 16.5 (3.0), 16.7 (3.3), and 17.0 (3.6) mmHg in the 15-μg bimatoprost implant group, and 17.4 (3.4), 17.1 (3.0), and 17.5 (3.7) mmHg in the timolol group.

Efficacy after Repeated Administration

The effects of bimatoprost implant on IOP were similar after repeated administration. Both dose strengths of bimatoprost implant demonstrated statistical and clinical noninferiority to timolol BID in lowering IOP in the 12 weeks after the second and third administrations (Fig S4, available at www.aaojournal.org).

In each treatment group, IOP was reduced throughout the study active treatment period. At week 52 (end of the active treatment period, 20 weeks after the last administration), 84.3% (167/198), 73.2% (145/198), and 86.4% (171/198) of subjects in the 10-μg bimatoprost implant, 15-μg bimatoprost implant, and timolol groups, respectively, remained in the study and had not received nonstudy IOP-lowering treatment in the study eye. The week 52 mean (standard deviation) diurnal IOP for these subjects was 18.1 (4.0) mmHg, 17.9 (3.9) mmHg, and 17.2 (3.4) mmHg, respectively.

Sustained Intraocular Pressure Control

Most subjects in the bimatoprost implant groups required no additional (nonstudy) IOP-lowering treatment in the study eye, even during the extended safety follow-up. A total of 137 subjects (69.2%) in the 10-μg bimatoprost implant group and 125 subjects (63.1%) in the 15-μg bimatoprost implant group reached month 20 without receiving any additional treatment in the study eye. In the timolol group, subjects continued to receive timolol BID throughout the extended follow-up, and 156 (78.8%) reached month 20 without receiving any additional treatment in the study eye. Study eyes that had not received any additional treatment demonstrated sustained IOP lowering throughout the extended follow-up (Fig 4).

Table 1. Baseline Demographics and Study Eye Characteristics (Intent-to-Treat Population)

Parameter	Bimatoprost Implant 10 μg (N = 198)	Bimatoprost Implant 15 μg (N = 198)	Timolol BID (N = 198)
Age, mean (SD), yrs	62.6 (11.5)	62.5 (13.0)	62.5 (11.0)
Range	23–88	25–92	24–88
Gender, n (%)			
Male	112 (56.6)	102 (51.5)	92 (46.5)
Female	86 (43.4)	96 (48.5)	106 (53.5)
Race/ethnicity, n (%)			
White	123 (62.1)	122 (61.6)	130 (65.7)
Black or African American	31 (15.7)	30 (15.2)	21 (10.6)
Hispanic	23 (11.6)	27 (13.6)	25 (12.6)
Asian	17 (8.6)	12 (6.1)	16 (8.1)
Other	4 (2.0)	6 (3.0)	5 (2.5)
Not reported	0	1 (0.5)	1 (0.5)
Iris color			
Brown	92 (46.5)	80 (40.4)	87 (43.9)
Dark brown	30 (15.2)	35 (17.7)	19 (9.6)
Hazel	11 (5.6)	8 (4.0)	13 (6.6)
Green	3 (1.5)	1 (0.5)	4 (2.0)
Blue	24 (12.1)	33 (16.7)	28 (14.1)
Gray	5 (2.5)	3 (1.5)	6 (3.0)
Green/brown	8 (4.0)	12 (6.1)	18 (9.1)
Blue/brown	16 (8.1)	23 (11.6)	20 (10.1)
Other heterochromatic	9 (4.5)	3 (1.5)	3 (1.5)
Diagnosis			
Open-angle glaucoma			
Primary	159 (80.3)	153 (77.3)	152 (76.8)
Pseudoexfoliation	1 (0.5)	1 (0.5)	1 (0.5)
Pigmentary	3 (1.5)	3 (1.5)	4 (2.0)
OHT	35 (17.7)	41 (20.7)	41 (20.7)
Lens status			
Phakic	152 (76.8)	131 (66.2)	145 (73.2)
Pseudophakic	46 (23.2)	67 (33.8)	53 (26.8)
CECD, mean (SD), cells/mm^2	2473 (342)	2453 (349)	2455 (306)
Range	1540–3396	1802–3373	1423–3419
Hour 0 IOP, mean (SD), mmHg	24.6 (2.7)	24.8 (2.8)	24.6 (2.6)
<25, n (%)	132 (66.7)	135 (68.2)	136 (68.7)
≥25, n (%)	66 (33.3)	63 (31.8)	62 (31.3)
Hour 2 IOP, mean (SD), mmHg	23.3 (3.1)	23.6 (3.1)	23.2 (2.9)

BID = twice daily; CECD = central corneal endothelial cell density; IOP = intraocular pressure; OHT = ocular hypertension; SD = standard deviation.

All study eyes that received additional treatment were prescribed topical IOP-lowering medication(s). One study eye (in the 15-μg bimatoprost implant group) also received a nonstudy IOP-lowering procedure, implantation of an ab interno gel stent, during the study.

Time to initial use of additional IOP-lowering treatment in the study eye after the last administration (i.e., the last administration before use of additional treatment) and after the third administration (for subjects who received 3 administrations and had not used additional treatment) was evaluated with Kaplan–Meier analysis (Fig 5). The estimated probability of not requiring additional treatment for 1 year after the last administration was 75.5% in 10-μg bimatoprost implant–treated eyes and 73.0% in 15-μg bimatoprost implant–treated eyes; the estimated probability of not requiring additional treatment for 1 year after the third administration was 82.1% in 10-μg bimatoprost implant–treated eyes and 87.8% in 15-μg bimatoprost implant–treated eyes. In study eyes in the timolol group, which continued to receive BID timolol throughout the study, the estimated probability of not requiring additional treatment for 1 year after the last sham administration was 88.9%, and the estimated probability of not requiring additional treatment for 1 year after the third sham administration was 95.2%.

Safety Analyses

The overall incidence of TEAEs during the 20-month study was 86.3% (170/197), 83.4% (161/193), and 70.1% (138/197), and the overall incidence of TEAEs that were considered by the investigator to be treatment related (i.e., possibly caused by the study treatment) was 57.9% (114/197), 61.1% (118/193), and 25.9% (51/197) in the 10-μg bimatoprost implant, 15-μg bimatoprost implant, and timolol groups, respectively. Almost all of the treatment-related TEAEs were ocular; ocular treatment-related TEAEs (the majority graded as mild or moderate in severity) were reported in the study eyes of 55.3% (109/197), 60.1% (116/193), and 24.4% (48/197) of subjects in the 10-μg bimatoprost implant, 15-μg bimatoprost implant, and timolol groups, respectively. Table S2 (available at www.aaojournal.org) lists TEAEs reported in study eyes at any time during the study. The most common TEAEs in study eyes were conjunctival hyperemia, eye irritation, foreign body sensation, and eye pain, which were typically reported as

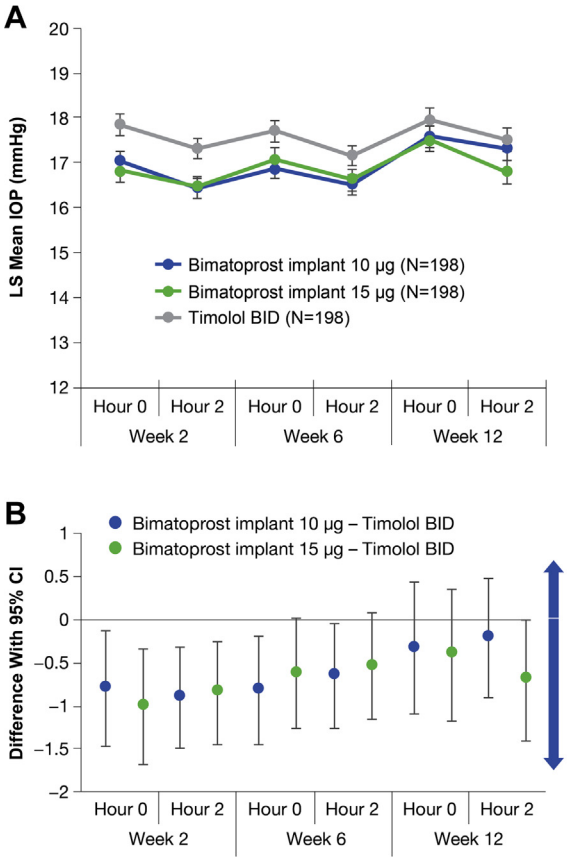

Figure 2. Primary end point of mean intraocular pressure (IOP) through week 12. **A,** Least-squares (LS) estimates of mean IOP in study eyes at hours 0 and 2 at weeks 2, 6, and 12 from a mixed-effect model for repeated measures (MMRM) model using observed values in the intent-to-treat population. The number of eyes censored from analysis at week 12 because of use of nonstudy IOP-lowering treatment was 2 of 198 (1.0%), 3 of 198 (1.5%), and 2 of 198 (1.0%) in the 10-µg bimatoprost implant, 15-µg bimatoprost implant, and timolol twice daily (BID) groups, respectively. **B,** Both dose strengths of bimatoprost implant met the prespecified criteria for statistical and clinical noninferiority to timolol BID. Bim = bimatoprost; CI = confidence interval.

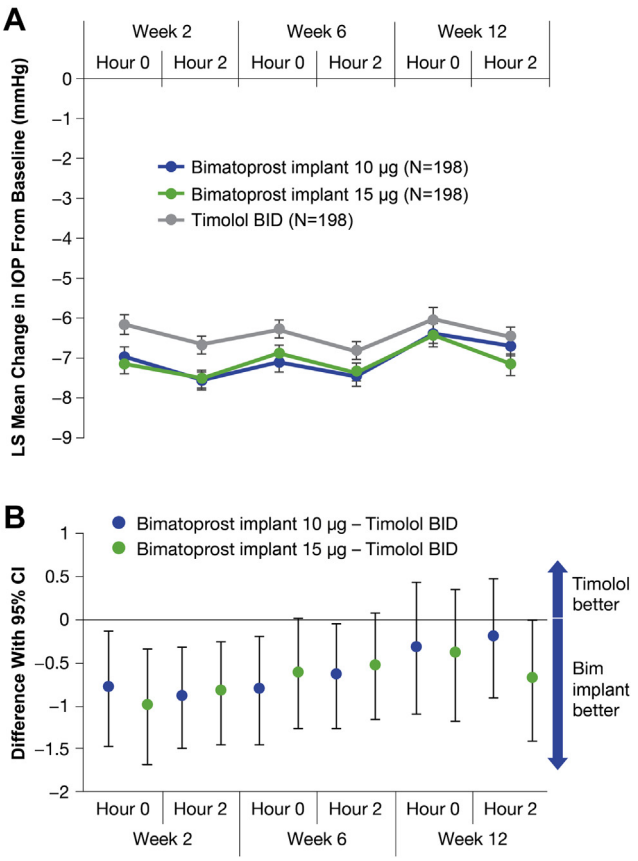

Figure 3. Primary end point of mean change in intraocular pressure (IOP) from baseline through week 12. **A,** Least-squares (LS) estimates of mean change in IOP from baseline in study eyes at hours 0 and 2 at weeks 2, 6, and 12 from a mixed-effect model for repeated measures (MMRM) model using observed values in the intent-to-treat population. The number of eyes censored from analysis at week 12 because of use of nonstudy IOP-lowering treatment was 2 of 198 (1.0%), 3 of 198 (1.5%), and 2 of 198 (1.0%) in the 10-µg bimatoprost implant, 15-µg bimatoprost implant, and timolol twice daily (BID) groups, respectively. **B,** Both dose strengths of bimatoprost implant met the prespecified criteria for statistical and clinical noninferiority to timolol BID. Bim = bimatoprost; CI = confidence interval.

procedure-related within 2 days after administration (Table 2), and were likely related to the implant and sham administration procedure preparation (e.g., use of povidone-iodine irrigation, which is standard of care to prevent infection during intraocular injections).

Corneal TEAEs of interest (primarily corneal endothelial cell loss and edema) and inflammatory TEAEs of interest (primarily iritis and anterior chamber cell) were more frequent in the bimatoprost implant groups than in the timolol group. There were no specific TEAE reports of "corneal decompensation" in any treatment group, although "corneal edema" was reported as a TEAE and can be viewed as a form of corneal decompensation. The incidence of serious ocular TEAEs was higher in the 10- and 15-µg bimatoprost implant groups (4.6% and 6.7%, respectively) than in the timolol group (0.5%). The most frequent serious ocular TEAE in both bimatoprost implant groups was corneal endothelial cell loss. There were 4 deaths during the study (1 in the 10-µg bimatoprost implant group, 2 in the 15-µg bimatoprost implant group, and 1 in the timolol group); each was unrelated to the study treatment.

Iris hyperpigmentation was reported as a TEAE in 6 subjects (3 in the 10-µg bimatoprost implant group, 2 in the 15-µg bimatoprost implant group, and 1 in the timolol group). There were no TEAE reports of eyelash growth or periorbital fat atrophy in any treatment group. However, eyelash and periorbital changes were not evaluated from photographs by a reading center.

The incidence of both corneal and inflammatory TEAEs of interest was higher with the 15-µg dose strength than with the 10-µg dose strength of implant. Although most TEAEs showed generally similar incidence rates after the first, second, and third implant administration, corneal TEAEs of interest occurred more frequently after repeated treatment. For example, in the 10- and 15-µg bimatoprost implant groups, respectively, corneal endothelial cell loss was reported after the initial administration in 0% (0/197) and 0.5% (1/193) of subjects, after the second administration in 1.6% (3/191) and 3.5% (6/172) of subjects, after the third administration (through the end of the week 52 visit window) in 3.3% (6/183) and 7.0% (11/158) of subjects, and during the 8-month extended follow-up in 5.1% (9/178) and 9.2% (14/152) of subjects who had received 3 administrations.

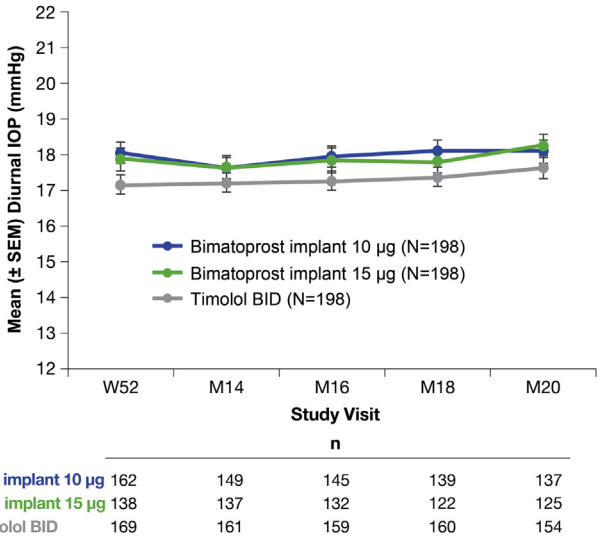

Figure 4. Mean diurnal intraocular pressure (IOP) in study eyes during the extended follow-up. The analysis used observed values and excluded measurements taken after use of any nonstudy IOP-lowering treatment. BID = twice daily; Bim = bimatoprost; M = month; SEM = standard error of the mean; W = week.

Implants were removed in 7 subjects (3.6%) in the 10-µg bimatoprost implant group and 16 subjects (8.3%) in the 15-µg bimatoprost implant group because of TEAEs, primarily corneal endothelial cell loss and edema. The implant removal for subjects in the 10-µg bimatoprost implant group was after the first, second, and third administrations in 1, 3, and 3 subjects, respectively, whereas for subjects in the 15-µg bimatoprost implant group, the implant removal was after the first, second, and third administrations in 1, 7, and 8 subjects, respectively. An additional subject in the 10-µg bimatoprost implant group underwent implant removal because of an administration procedure error (the subject had received 2 implant administrations on day 1; 1 of the implants was removed the following day).

Evaluation of CECD by specular microscopy showed a time-dependent and dose strength-dependent decrease in mean CECD in study eyes in both bimatoprost implant groups, with greater loss in CECD in the 15-µg group (Table 3). The loss in mean CECD from baseline to month 20 was approximately 6% in study eyes treated with the 10-µg dose strength, approximately 2% in study eyes treated with BID timolol, and approximately 1% in all fellow eyes treated with BID timolol (Fig 6). In the 10-µg and 15-µg bimatoprost implant groups, respectively, a ≥20% decrease in CECD from baseline was seen in 0% (0/187) and 2.8% (5/181) of study eyes at 12 weeks after the initial administration (week 12), in 2.3% (4/177) and 6.3% (10/159) of study eyes at 12 weeks after the second administration (week 28), in 4.1% (7/169) and 12.3% (18/146) of study eyes at 12 weeks after the third administration (week 44), and in 10.2% (20/196) and 21.8% (42/193) of study eyes at the month 20 or last study visit before exit. In the timolol group, a ≥20% decrease in CECD from baseline was seen in no study eyes at 12 weeks after the first, second, or third administration and in 0.5% (1/197) of study eyes at the month 20 or last study visit before exit.

There were no clinically significant changes in mean central corneal thickness (CCT) during the study period in any treatment group. Mean study eye changes in CCT from baseline were consistently <5 µm throughout the study in all treatment groups. Among subjects with corneal TEAEs of interest in the bimatoprost implant groups, the mean study eye change in CCT from baseline at the last available study visit was similarly <5 µm and considered not clinically significant. Mean BCVA was stable from baseline to the last available visit, both overall in each treatment group, and in eyes with corneal TEAEs of interest (Table 4). Among subjects with corneal TEAEs of interest, 1 in the 10-µg group and 2 in the 15-µg group had >2-line BCVA loss at their last study visit (Table 4).

Discussion

Both tested dose strengths of bimatoprost implant met the primary end points in this study and were noninferior to BID topical timolol in lowering IOP through 12 weeks. Two repeated administrations of bimatoprost implant at 16-week intervals demonstrated similar efficacy in lowering IOP. After the third administration in the bimatoprost implant treatment groups, IOP was controlled in most subjects for at least 1 year without any additional treatment. The safety profile of the implant, based on 3 administrations at 16-week intervals, was better with the 10-µg dose strength compared with the 15-µg dose strength.

In this 20-month study, there were few TEAE reports of iris pigmentation and none of eyelash growth, eyelash pigmentation, skin pigmentation, or periorbital fat atrophy. These results are consistent with results of the small 2-year, phase 1/2 study of bimatoprost implant, in which there were no reports of iris pigmentation, eyelash growth, or periorbital fat atrophy in eyes treated with bimatoprost implant, despite the occurrence of these adverse events in fellow eyes treated with topical bimatoprost.[23] The results are also consistent with the nonclinical drug distribution study in dogs,[21] in which drug levels in ocular surface and periocular tissues after bimatoprost implant administration were undetectable or decreased compared with drug levels after topical administration of bimatoprost 0.03%. In other safety findings, the incidence of corneal adverse events was much lower in the phase 1/2 study[23] than in the present study, probably because subjects in the phase 1/2 study received a single implant administration or a single additional, as-needed administration, whereas in the present study, subjects received 3 administrations at 4-month intervals.

Comparison of findings from the phase 1/2 and phase 3 studies suggests that when more implants occupy the inferior angle in a short period of time, there is greater potential for endothelial cell contact and loss. In the 24-month phase 1/2 study, among study eyes with CECD data, 0% (0/17) treated with 10-µg implant and 12.5% (2/16) treated with 15-µg implant had a ≥20% loss in CECD during the study (Allergan, data on file). For subjects who received 2 administrations, the mean interval between administrations was 6.6 and 6.2 months (range, 98–351 days and 120–316 days) in the 10-µg and 15-µg groups, respectively (Allergan, data on file). In the present phase 3 study using fixed administration every 4 months, rates of ≥20% CECD loss at month 20 or study exit were higher (10.2% and 21.8% in the 10-µg and 15-µg groups, respectively), and 3 bimatoprost implant–treated subjects with corneal TEAEs (1 in the

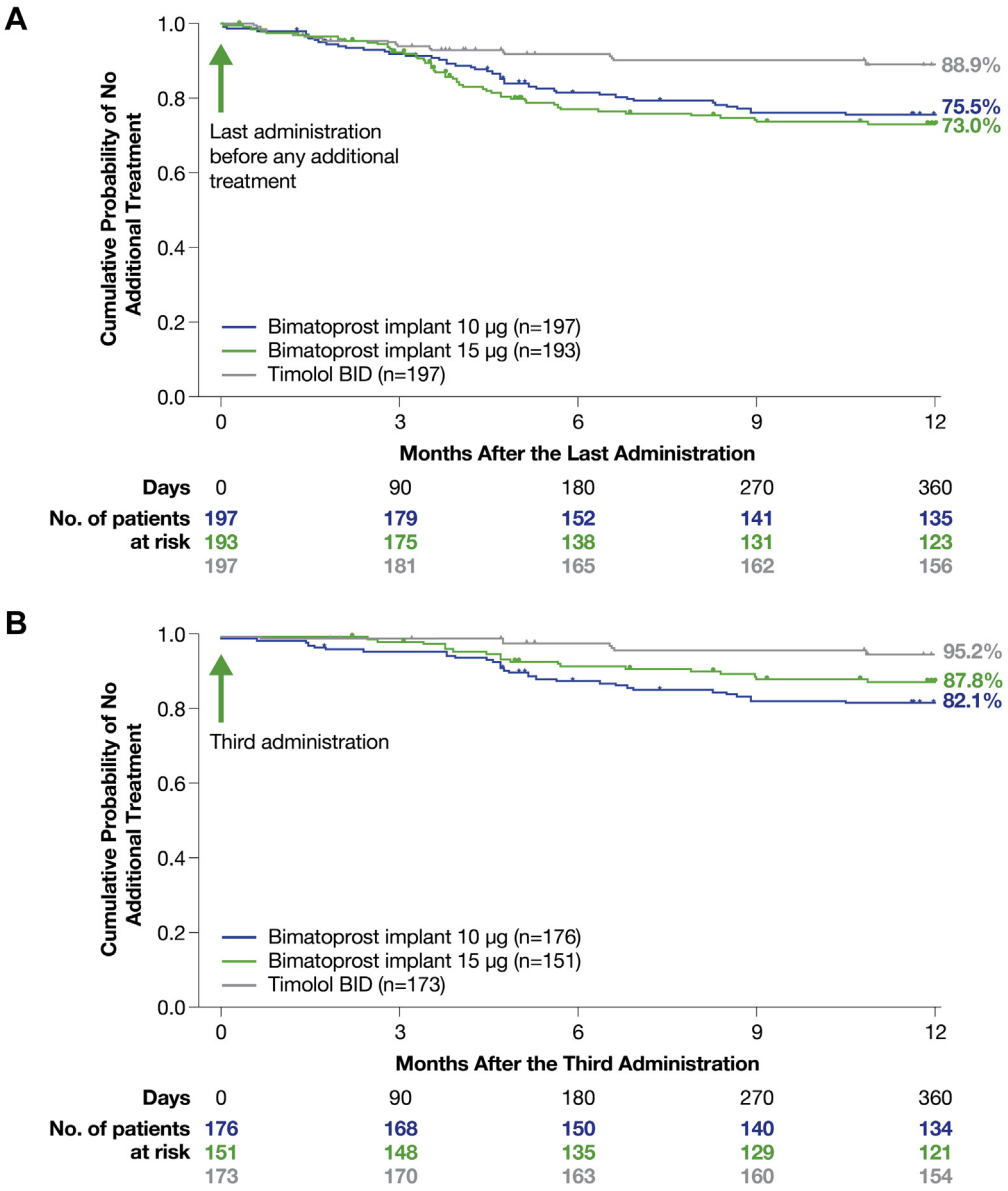

Figure 5. Kaplan–Meier survival analysis of time to initial use of additional intraocular pressure (IOP)-lowering treatment in the study eye after the last bimatoprost implant or sham administration **(A)** and after the third administration in subjects who received 3 administrations **(B)**. BID = twice daily.

10-µg group and 2 in the 15-µg group) had >2-line BCVA loss at their last visit.

Treatment with an intracameral PGA implant offers several potential advantages over topical PGA dosing for lowering IOP. The targeted delivery of PGA to outflow tissues with an intracameral implant bypasses the ocular surface and may reduce the likelihood of some adverse effects[8,25] associated with topical administration of PGAs. In addition, patient adherence to glaucoma medication may be improved with a dropless therapy that does not require daily administration, potentially leading to improved visual function outcomes. Furthermore, long-term, sustained IOP lowering with an implant can be expected to reduce the burden of treatment for patients and their caregivers.

In this study, subjects received 3 administrations at 16-week intervals, and after the third administration, the probability of not requiring additional IOP-lowering treatment for 1 year was 82.1% with the 10-µg dose strength and 87.8% with the 15-µg dose strength. By comparison, in the phase 1/2 dose escalation study of the safety and efficacy of bimatoprost implant, sustained IOP lowering after a single administration of a 6-, 10-, 15-, or 20-µg dose strength of implant was demonstrated in a subset of subjects, with 40% of subjects requiring no additional IOP-lowering treatment for up to 1 year and 28% of subjects requiring no additional IOP-lowering treatment for up to 2 years.[23] The probability of not requiring additional treatment for 1 year after a single implant administration in the phase 1/2 study was 36% (Weinreb RN, Walters T, Bejanian M, et al. Duration of

Table 2. Treatment-Emergent Ocular Adverse Events in Study Eyes by Time of Onset after Bimatoprost Implant or Sham Administration*

TEAE, n (%)	Onset within 2 Days			Onset after 2 Days		
	Bimatoprost Implant 10 μg (N = 197)	*Bimatoprost Implant 15 μg (N = 193)*	*Timolol BID (N = 197)*	*Bimatoprost Implant 10 μg (N = 197)*	*Bimatoprost Implant 15 μg (N = 193)*	*Timolol BID (N = 197)*
Conjunctival hyperemia	54 (27.4)	61 (31.6)	35 (17.8)	18 (9.1)	33 (17.1)	15 (7.6)
Eye irritation	15 (7.6)	23 (11.9)	20 (10.2)	3 (1.5)	4 (2.1)	1 (0.5)
Foreign body sensation	19 (9.6)	22 (11.4)	11 (5.6)	5 (2.5)	12 (6.2)	0
Eye pain	21 (10.7)	17 (8.8)	8 (4.1)	4 (2.0)	7 (3.6)	1 (0.5)
Corneal endothelial cell loss	0	0	0	17 (8.6)	31 (16.1)	0
Dry eye	10 (5.1)	7 (3.6)	6 (3.0)	11 (5.6)	11 (5.7)	6 (3.0)
Photophobia	16 (8.1)	19 (9.8)	3 (1.5)	6 (3.0)	6 (3.1)	1 (0.5)
Conjunctival hemorrhage	12 (6.1)	11 (5.7)	10 (5.1)	2 (1.0)	4 (2.1)	2 (1.0)
Punctate keratitis	10 (5.1)	14 (7.3)	10 (5.1)	1 (0.5)	3 (1.6)	6 (3.0)
IOP increased	1 (0.5)	1 (0.5)	0	16 (8.1)	10 (5.2)	7 (3.6)
Vision blurred	9 (4.6)	8 (4.1)	9 (4.6)	1 (0.5)	3 (1.6)	2 (1.0)
Iritis	7 (3.6)	13 (6.7)	0	4 (2.0)	9 (4.7)	1 (0.5)
Lacrimation increased	8 (4.1)	5 (2.6)	10 (5.1)	0	7 (3.6)	2 (1.0)
Corneal edema	1 (0.5)	1 (0.5)	0	6 (3.0)	13 (6.7)	2 (1.0)
Anterior chamber cell	5 (2.5)	5 (2.6)	0	3 (1.5)	8 (4.1)	0
Ocular discomfort	4 (2.0)	4 (2.1)	2 (1.0)	1 (0.5)	4 (2.1)	0
Visual field defect	0	0	0	8 (4.1)	4 (2.1)	3 (1.5)
Iris adhesions	0	0	0	4 (2.0)	6 (3.1)	4 (2.0)
Aqueous humor leakage	3 (1.5)	5 (2.6)	0	0	0	0
Blepharitis	1 (0.5)	0	0	2 (1.0)	4 (2.1)	2 (1.0)
Cataract	0	0	0	2 (1.0)	4 (2.1)	2 (1.0)
Conjunctival edema	0	1 (0.5)	2 (1.0)	1 (0.5)	3 (1.6)	1 (0.5)
Corneal opacity	1 (0.5)	0	0	0	6 (3.1)	1 (0.5)
Corneal touch	0	0	0	5 (2.5)	3 (1.6)	0
Anterior chamber flare	1 (0.5)	1 (0.5)	0	1 (0.5)	5 (2.6)	0
Visual acuity reduced	0	1 (0.5)	0	1 (0.5)	5 (2.6)	0
Corneal dystrophy	0	0	0	0	5 (2.6)	1 (0.5)
Vitreous detachment	0	0	0	1 (0.5)	4 (2.1)	1 (0.5)
Drug delivery device implantation	0	0	0	0	5 (2.6)	0
Macular fibrosis	0	0	0	1 (0.5)	0	4 (2.0)
Overall†	95 (48.2)	108 (56.0)	76 (38.6)	93 (47.2)	113 (58.5)	65 (33.0)

BID = twice daily; IOP = intraocular pressure; TEAE = treatment-emergent adverse event.
*All ocular TEAEs in study eyes that were reported in ≥2% of subjects in any treatment group within 2 days or after 2 days following administration are listed.
†Any ocular TEAE in the study eye.

effect of intracameral bimatoprost sustained-release implant [Bimatoprost SR; BimSR] in phase 1/2 and phase 3 clinical studies. Presentation at the American Society of Cataract and Refractive Surgery American Society of Ophthalmic Administrators Annual Meeting, May 3–7, 2019, San Diego, CA). The greater probability of long-term, sustained IOP lowering in the present study likely resulted from sequential implant administrations producing a longer cumulative duration of exposure to high drug concentrations in target tissues.

The extended duration of IOP lowering after bimatoprost implant administration is unlikely to be explained by

Table 3. Mean (Standard Deviation) Central Corneal Endothelial Cell Density in Study Eyes on Specular Microscopy, Cells/mm^2

Visit	Bimatoprost Implant 10 μg (N = 197)	Bimatoprost Implant 15 μg (N = 193)	Timolol BID (N = 197)	All Fellow Eyes (N = 587)
Baseline	2471.7 (342.6) n = 197	2456.1 (352.4) n = 193	2454.7 (307.1) n = 197	2448.9 (361.3) n = 586
Week 12	2440.8 (352.3) n = 187	2436.6 (386.9) n = 181	2448.6 (310.5) n = 189	2441.6 (359.9) n = 557
Week 28	2416.4 (403.8) n = 177	2357.3 (463.2) n = 159	2446.8 (316.3) n = 179	2437.3 (364.7) n = 515
Week 44	2390.1 (419.1) n = 169	2299.4 (512.7) n = 146	2418.9 (323.6) n = 167	2441.6 (365.6) n = 484
Week 52	2395.4 (413.6) n = 171	2264.3 (550.5) n = 145	2425.6 (321.4) n = 171	2446.5 (361.8) n = 489
Month 20	2316.4 (484.1) n = 168	2155.2 (585.8) n = 143	2409.0 (313.3) n = 164	2433.7 (357.2) n = 477

BID = twice daily.

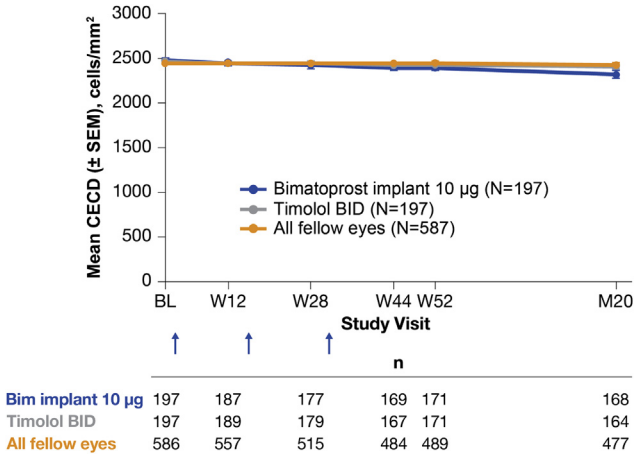

Figure 6. Mean corneal endothelial cell density (CECD) in study eyes treated with bimatoprost implant 10 µg and timolol twice daily (BID). The timing of implant or sham administration is shown with **arrows**. Error bars show standard error of the mean. Bim = bimatoprost; BL = baseline; M = month; SEM = standard error of the mean; W = week.

continued drug presence beyond 3−4 months after administration. In vitro assays determined that drug release from the implant is complete within 90 days (Fig S1, available at www.aaojournal.org), and pharmacokinetics studies of bimatoprost implant in a normotensive beagle dog animal model showed that drug release is complete and intraocular tissue drug levels are below the limits of detection by 4.2 months after implant administration (Table S3, available at www.aaojournal.com). Consistent with these results, in the present study, drug concentrations in aqueous humor samples taken from 2 subjects during implant removal were below the limit of quantitation (<0.05 ng/ml) at 100 and 114 days after their last implant administration. These findings suggest that there was no drug present during the extended follow-up period after week 52, yet IOP continued to be controlled in the majority of subjects up to month 20.

The extended duration of effect of bimatoprost implant on IOP potentially may be explained by durable matrix metalloproteinase (MMP)-mediated remodeling of aqueous humor outflow pathways.[23,26] The mechanism of IOP lowering by PGAs is believed to involve concentration-dependent upregulation of MMP expression and activity in the ciliary body and trabecular meshwork, resulting in increased extracellular matrix turnover and decreased resistance to aqueous outflow through unconventional (uveoscleral) and conventional (trabecular meshwork) pathways.[27-32] In human ciliary body cells in vitro, a clear dose response for upregulation of MMPs is seen with increasing bimatoprost acid concentration—the higher the drug concentration (within the range achieved by bimatoprost implant in the ciliary body in animal models[21]), the higher the MMP expression.[32] Long-term treatment with topical bimatoprost has been shown to cause changes in morphology in the ciliary body and trabecular meshwork consistent with formation of new outflow channels and enhanced outflow in a nonhuman primate model.[33] We hypothesize that the targeted delivery and higher concentrations of bimatoprost achieved in outflow tissues with the intracameral implant compared with topical dosing cause greater upregulation of MMP activity in the target tissues and more durable tissue remodeling, resulting in sustained IOP lowering.[23,26] Other potential explanations for sustained IOP lowering in bimatoprost implant−treated eyes, although unlikely, could include medication mix-up or use of the timolol drop intended for use in the fellow eye in the study eye.

The polymer matrix of bimatoprost implant was designed to biodegrade slowly to avoid inflammation, peripheral anterior synechiae, and scarring in the angle that can be caused by rapidly degrading polymer (Allergan, data on file). Chronic inflammation was not a significant concern in this study: iritis was reported infrequently after the 2-day postprocedure period, and the incidence of iris adhesions was similar in the bimatoprost implant and topical timolol treatment groups. The implant degraded over time with some variability among subjects in the rate of implant biodegradation. Because 3 implants were administered at fixed 4-month treatment intervals, the slow biodegradation allowed as many as 3 implants to be present at the same time in some eyes. However, the majority of the implants decreased to ≤50% of their original size by week 44 and to ≤25% of their original size by week 52, and by month 20, no implant was visible in 14%−16% of subjects. A long-term study in progress (NCT03891446) is evaluating the

Table 4. Best-Corrected Visual Acuity in Study Eyes

	All Subjects			Subjects with Corneal TEAE of Interest*		
Safety Parameter	*Bim Implant 10 µg (N = 197)*	*Bim Implant 15 µg (N = 193)*	*Timolol BID (N = 197)*	*Bim Implant 10 µg (N = 23)*	*Bim Implant 15 µg (N = 42)*	*Timolol BID (N = 3)*
Mean BCVA (SD), letters						
Baseline	82.5 (5.2)	82.8 (5.1)	82.2 (5.2)	82.2 (5.4)	82.3 (5.1)	86.7 (2.9)
Month 20 or last visit	83.0 (6.0)	82.6 (5.8)	82.8 (6.4)	82.4 (6.2)	81.4 (5.9)	86.7 (2.9)
Subjects with >2-line (10-letter) loss in BCVA from baseline at month 20 or last visit, n (%)	4 (2.0)	3 (1.6)	2 (1.0)	1 (4.3)	2 (4.8)	0 (0)

BCVA = best-corrected visual acuity; BID = twice daily; Bim = bimatoprost; SD = standard deviation; TEAE = treatment-emergent adverse event.
*All subjects with a TEAE report of corneal endothelial cell loss, corneal edema, corneal opacity, corneal touch, corneal disorder, or corneal thickening.

safety of repeated implant administration in the presence of small remnant implants.

Many of the most common TEAEs (e.g., conjunctival hyperemia and eye irritation) in study eyes in all treatment groups were reported within 2 days after the administration procedure, were considered to be procedure-related, and were likely caused by the procedure preparation, which included povidone-iodine irrigation. Notably, there was no requirement for postprocedure use of topical ophthalmic nonsteroidal anti-inflammatory drugs or corticosteroids that could mask the hyperemia and ocular irritation caused by ophthalmic surgical preparation materials.

The rate of corneal TEAEs of interest was higher with the 15-μg dose strength of implant, which is approximately 50% longer than the 10-μg implant. Furthermore, the rate of corneal TEAEs of interest (but not other TEAEs) increased with each subsequent administration. These findings suggest that the events likely occurred secondary to a physical interaction between the implant(s) and the cornea. Consistent with the premise that accumulation of polymer matrix in the angle could cause corneal endothelial cell loss in some cases, the reduction in mean CECD in this study, particularly with the 15-μg implant, was larger than the 3% reduction seen after 1 or 2 administrations of bimatoprost implant (all dose strengths pooled) in the phase 1/2 study.[23] The safety profile of bimatoprost implant was improved, and corneal endothelial cell loss was reduced, with the smaller 10-μg implant. Eight subjects in the 10-μg bimatoprost implant group compared with 16 subjects in the 15-μg bimatoprost implant group underwent implant removal; the reasons for implant removal were TEAEs in 7 subjects and an administration procedure error in 1 subject in the 10-μg group, and TEAEs in all 16 subjects in the 15-μg group. Implant removal should be avoided when possible because of the increased risk of adverse events associated with intraocular procedures, such as endophthalmitis, iritis, and lens and corneal damage. However, because the implants are placed intracamerally, removal is a straightforward procedure in which they are flushed out of the eye under sterile conditions using an intraocular ophthalmic irrigating solution, with or without use of a viscosurgical device, through a keratome incision. We observed that in general, corneal TEAEs resolved after implant removal, and CECD stabilized in subjects who had undergone corneal endothelial cell loss.

In the present study, a dose-response was observed, with the 15-μg dose strength demonstrating slightly better efficacy in mean IOP lowering and time to use of additional treatment after the third administration. However, given the study dosing regimen of 3 implant administrations at fixed 16-week intervals, the 10-μg dose strength had a better overall safety profile. Interim results from an ongoing phase 3 study with an identical protocol (ARTEMIS 2, NCT02250651), which is estimated to be completed in March 2020, were confirmatory. Because the benefit-risk assessment favored the 10-μg dose strength, a new drug application was filed with the US Food and Drug Administration, and bimatoprost implant 10 μg has received regulatory approval for single intracameral administration for the reduction of IOP in patients with OAG or OHT.[34] On the basis of its demonstrated safety profile, bimatoprost implant should be used with caution in patients with limited corneal endothelial cell reserve and in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.[34] Ongoing studies (NCT03850782, NCT03891446) are evaluating the safety and efficacy of longer administration intervals with as-needed administration.

Regulatory approval of the 10-μg dose strength, from a safety viewpoint, was based on the demonstration in the phase 1/2 and phase 3 studies that 0 subjects had $\geq$20% endothelial cell loss after single administration of 10-μg bimatoprost implant. In the phase 1/2 study, these subjects were followed for up to 2 years after a single administration as the implant biodegraded over time, and no subjects had $\geq$20% endothelial cell loss. Because of the large safety margin with a single implant, there is no regulatory requirement of specular microscopy monitoring in the bimatoprost implant prescribing information. Use of bimatoprost implant with multiple administrations would be off-label at the time of publication, and this is currently not recommended.

One study limitation is that the study protocol did not specify an IOP or percentage IOP reduction requiring use of nonstudy IOP-lowering medication. In addition, it was not possible to evaluate a potential relationship between the response to bimatoprost implant in this study and subjects' previous response to topical bimatoprost (or any PGA), because data on subjects' previous responses to topical PGAs (if used previously) were not collected. Moreover, although the implant administration schedule in this study was developed on the basis of previous study data to maintain a consistent IOP reduction, allowing comparisons with the control arm (daily topical treatment), the requirement for administration of 3 implants at 16-week intervals was also a study limitation. The results suggest that subjects could have achieved sustained IOP lowering with fewer implants or with administration at longer intervals. Furthermore, the occurrence of corneal events in some subjects appeared to be related to accumulation of implant material in the iridocorneal angle, and these corneal events may have been abated with less frequent administration. Because of the sustained IOP-lowering effects of bimatoprost implant, the interval between administrations is expected to be substantially longer for the majority of patients in real-world practice. A flexible re-treatment paradigm based on administration when necessary to maintain adequate IOP control is, therefore, an appropriate prescribing approach that will reduce risk and treatment burden without compromising efficacy.

In summary, this study demonstrated effective IOP lowering with bimatoprost implant in a large, diverse population with OAG and OHT. Corneal and inflammatory TEAEs of interest (e.g., corneal endothelial cell loss and iritis) were more frequent in the bimatoprost implant groups than in the timolol group. The study results may be generalizable to patients with characteristics similar to those of the study population (i.e., patients with open angles and CECD of $\geq$1800 cells/mm^2). The smaller size of the 10-μg dose strength of the implant was associated with an

improved safety profile, and the benefit-risk assessment in this study was favorable for bimatoprost implant 10 μg. Continuous drug delivery to target tissues with the implant resulted in sustained IOP lowering, with the vast majority of subjects requiring no additional IOP-lowering treatment for 1 year after the third administration. Use of the intracameral bimatoprost implant has the potential to decrease patient treatment burden and improve treatment adherence in glaucoma.

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HUMAN SUBJECTS: Human subjects were included in this study. The study adhered to the tenets of the Declaration of Helsinki and was conducted in conformance with the International Conference on Harmonization E6 guideline for Good Clinical Practice or the laws and regulations of the country in which the research was conducted. All participants provided informed consent.

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **BID** = twice daily; **CECD** = corneal endothelial cell density; **CI** = confidence interval; **IOP** = intraocular pressure; **MMP** = matrix metalloproteinase; **MMRM** = mixed-effect model for repeated measures; **OAG** = open-angle glaucoma; **OHT** = ocular hypertension; **PGA** = prostaglandin analog; **TEAE** = treatment-emergent adverse event.

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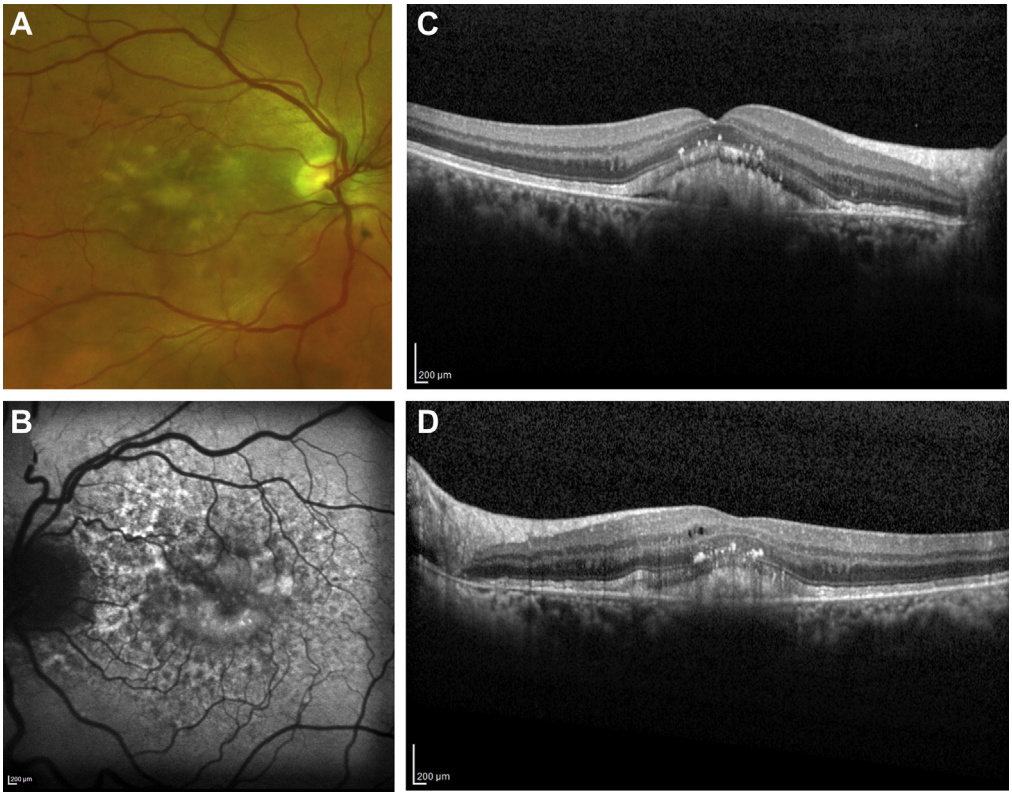
Pictures & Perspectives



Large Subfoveal Vitelliform Lesions in a Case of Pentosan Polysulfate Maculopathy

Pentosan polysulfate (Elmiron; Janssen, Horsham, PA) toxicity is typically characterized by centrifugally spreading coarse macular and parapapillary retinal pigment epithelium alterations, reticular lipofuscin accumulation, and rarely small vitelliform lesions. It may be confused with or overlap pattern dystrophy and age-related macular degeneration. A 65-year-old woman was administered 200 mg of pentosan polysulfate twice daily for 15 years for interstitial cystitis presented with large, subfoveal, hyperautofluorescent vitelliform lesions (Fig **A**, **B**), elongated photoreceptor outer segments (Fig **C**, **D**), and intraretinal hyperreflectivities on OCT. Genetic testing revealed a variant of unknown significance in *ABCA4*, but it is unclear what role this played in lipofuscin accumulation. (Magnified version of Fig **A**-**D** is available online at www.aaojournal.org).

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