Bimatoprost Sustained-Release Implants for Glaucoma Therapy: 6-Month Results From a Phase I/II Clinical Trial

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• PURPOSE: To evaluate the safety and intraocular pressure (IOP)-lowering effect of a biodegradable bimatoprost sustained-release implant (Bimatoprost SR).

• DESIGN: Phase I/II, prospective, 24-month, dose-ranging, paired-eye controlled clinical trial.

• METHODS: At baseline following washout, open-angle glaucoma patients (n = 75) were administered Bimatoprost SR (6 μg, 10 μg, 15 μg, or 20 μg) intracamerally in the study eye; the fellow eye began topical bimatoprost 0.03% once daily. Rescue topical IOP-lowering medication or a single repeat treatment with implant was allowed. The primary endpoint was IOP change from baseline. The main safety measure was adverse events. Results through month 6 are reported.

• RESULTS: Bimatoprost SR provided rapid, sustained IOP lowering. Overall mean IOP reduction from baseline through week 16 in study eyes was 7.2, 7.4, 8.1, and 9.5 mm Hg with the 6-μg, 10-μg, 15-μg, and 20-μg dose strengths of implant, respectively, vs 8.4 mm Hg in topical bimatoprost-treated pooled fellow eyes (data censored at rescue/retreatment). Rescue/retreatment was not required in 91% and 71% of study eyes up to week 16 and month 6, respectively. Adverse events in study eyes usually occurred within 2 days after the injection procedure and were transient. Conjunctival hyperemia with onset later than 2 days after the injection procedure was more common with topical bimatoprost than Bimatoprost SR (17.3% vs 6.7% of eyes).

• CONCLUSIONS: Bimatoprost SR demonstrated favorable efficacy and safety through 6 months. All dose strengths were comparable to topical bimatoprost in overall IOP reduction through week 16. A single administration controlled IOP in the majority of patients for up to 6 months. (Am J Ophthalmol 2017;175:137–147. © 2016 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

OPEN-ANGLE GLAUCOMA IS A CHRONIC BLINDING disease estimated to affect more than 40 million individuals worldwide.[1] The preferred initial treatment is usually topical ocular hypotensive medication to lower intraocular pressure (IOP) and reduce the risk of vision loss, but adherence to topical glaucoma medication is poor. Nonadherence of patients to treatment regimens is endemic in chronic, symptomatic disease and is associated with worse outcomes[2,3] and, frequently, with increased health care utilization and costs.[4,5] Pharmacy claims data have shown that adherence to topical IOP-lowering medication is worse than adherence to oral medications used to treat hypertension and diabetes, with patients filling prescriptions and having prostaglandin/prostamide glaucoma medication available for dosing only 37% of the days in a year.[6] Barriers to adherence to topical glaucoma medication include forgetfulness, difficulty in eye drop administration, dosing frequency, lack of understanding of the disease, medication cost, and side effects.[7–9] Poor adherence is associated with greater loss of vision in glaucoma patients.[10,11] Therefore, the costs of poor adherence in glaucoma include the financial burden and reduced quality of life associated with impaired vision and blindness, as well as the increase in health care expenditures for medical care and surgery in advanced-stage glaucoma.[12]

Sustained-release intraocular drug delivery has the potential to provide long-term IOP lowering in glaucoma without the need for topical administration. This approach would reduce a number of barriers to adherence in the glaucoma population. For example, sustained-release intraocular drug delivery may be appropriate for the many elderly glaucoma patients who lack the hand strength, steadiness, and dexterity to squeeze a medication bottle and dispense a single drop into the eye. Adverse effects following topical administration caused by drug and/or preservative exposure to the

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ocular surface and surrounding tissues, such as worsening of dry eye symptoms[13] and periocular skin discoloration,[14] may also be minimized with this approach.

Bimatoprost is a prostaglandin analogue (PGA) that effectively reduces IOP when administered topically.[15] A biodegradable bimatoprost sustained-release implant (Bimatoprost SR) has been developed to address the problem of nonadherence in glaucoma and the unmet medical needs of patients with open-angle glaucoma who are intolerant or incapable of using topical glaucoma medications. Bimatoprost SR consists of bimatoprost in the biodegradable NOVADUR (Allergan plc, Dublin, Ireland) platform for drug delivery.[16] The implant is designed to be placed intracamerally in the eye and provide slow release of bimatoprost over time.

Bimatoprost SR is currently being evaluated in patients with open-angle glaucoma in a 2-year, phase I/II study. The study objectives are to evaluate the safety and IOP-lowering effects of Bimatoprost SR and to determine the dose strength of Bimatoprost SR that has an IOP-lowering effect similar to bimatoprost 0.03% ophthalmic drops. We report here 6-month interim safety and efficacy outcomes in patients who received Bimatoprost SR (Generation 2 formulation) containing a 6-μg, 10-μg, 15-μg, or 20-μg dose of bimatoprost.

METHODS

• **STUDY DESIGN:** This ongoing, 24-month, phase I/II, open-label, multicenter, dose ranging, paired-eye comparison study is registered as NCT01157364 at www.ClinicalTrials.gov. The conduct of the study is in compliance with Good Clinical Practice and the Health Insurance Portability and Accountability Act of 1996. Patients were compensated for their participation in the study in accordance with the US Food and Drug Administration guidance statement on payment to research subjects in studies (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm). An institutional review board or ethics committee approved the study protocol at each site before the study began, and all patients provided written informed consent before undergoing any study-related procedure.

The study was planned to have an adaptive process with emerging data from the trial used to guide dose selection and protocol amendments as the study continued. During the study, the formulation of Bimatoprost SR was optimized to modify the rate of the polymer matrix biodegradation and drug release, and this Generation 2 implant was introduced into the clinical trial. This report presents the 6-month interim results using the optimized Generation 2 implant.

• **STUDY POPULATION:** Patient eligibility criteria included the following: at least 18 years of age; diagnosis of open-angle glaucoma in the study eye with >1 dB and <17 dB of mean deviation visual field loss; diagnosis of open-angle glaucoma or ocular hypertension in the fellow eye that in the investigator's opinion could be treated adequately with topical bimatoprost 0.03% monotherapy; history of at least 20% IOP lowering in response to topical PGA ocular hypotensive medication; and, in the investigator's opinion, would not be at significant risk during the study washout or treatment period. The iridocorneal angle inferiorly in the study eye was required to be Shaffer grade 3 or greater based on gonioscopy and sufficient to fit an implant without corneal endothelial cell touch on optical coherence tomography (OCT), as determined by an independent reading center. IOP in both eyes after washout was required to be between 22 mm Hg and 36 mm Hg, with a difference between eyes of no more than 3 mm Hg, at 8 AM (± 1 hour) at the baseline visit.

Key exclusion criteria included the following: history of narrow-angle or closed-angle glaucoma; cataract surgery resulting in a posterior capsule tear; intraocular surgery within the 3 months before the study treatment; history of refractive surgery; conjunctival hyperemia or other ocular surface findings of greater than trace severity on biomicroscopic examination at baseline; history of conjunctival hyperemia of greater than mild severity or iris color changes associated with topical PGA treatment; central corneal thickness <470 μm or >630 μm (or a difference between eyes >70 μm); and central endothelial cell count <2000 cells/mm^2 by specular microscopy.

• **INTERVENTION AND VISIT SCHEDULE:** A schematic of the study design is shown in Figure 1. Patients who were using topical ocular hypotensive medication in either eye at screening (day −42 to −4) discontinued the medication before the baseline visit (day −3 to −1). Required washout periods were 4 days for parasympathomimetics and carbonic anhydrase inhibitors, 14 days for sympathomimetics and alpha-adrenergic agonists, and 28 days for beta-adrenergic antagonists, prostaglandin analogues, and fixed-combination products. If both eyes met the entry criteria at baseline, the eye with the higher IOP (or, if the IOP was the same in both eyes, the eye with the larger iridocorneal angle width as determined by OCT) was selected as the study eye. On day 1, the study eye was prepared for intraocular injection according to standard clinical practice, with administration of a broad-spectrum topical antibiotic followed by topical anesthetic, and irrigation of the conjunctival surface with povidone-iodine 5% ophthalmic solution. Bimatoprost SR implant (6-μg, 10-μg, 15-μg, or 20-μg dose Generation 2 formulation) was administered intracamerally to the study eye as shown in the Supplemental Animation (Supplemental Material at AJO.com) using a single-use, prefilled 28 gauge applicator system (Figure 2). A single implant that varied in size was administered to achieve the 6-μg, 10-μg, and 15-μg dose strengths; two 10-μg implants were

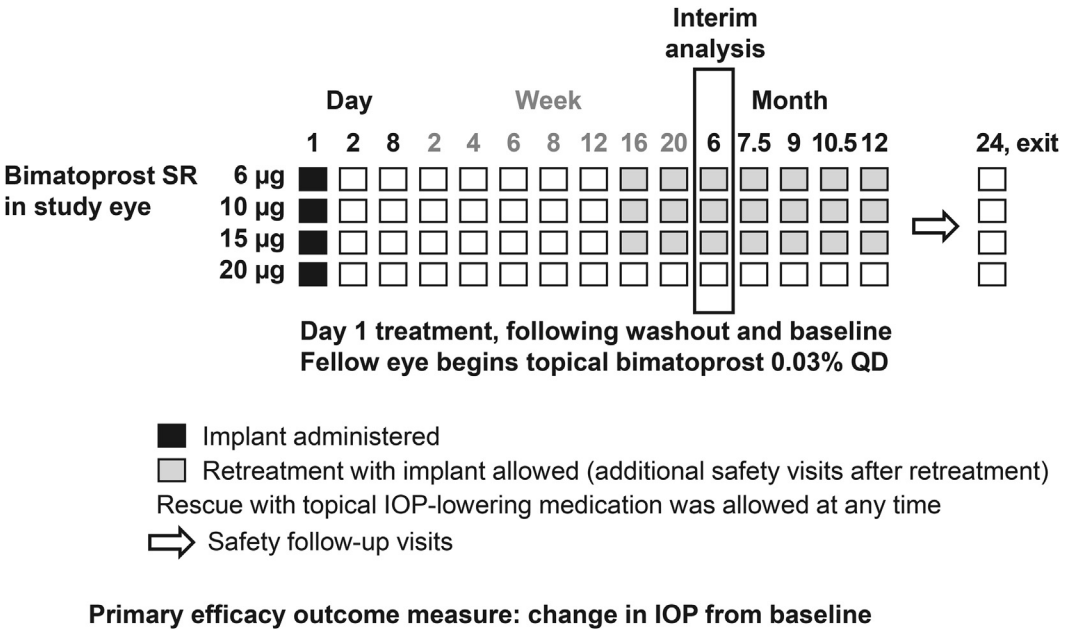


FIGURE 1. Study design. Bimatoprost SR = bimatoprost sustained-release implant; IOP = intraocular pressure.

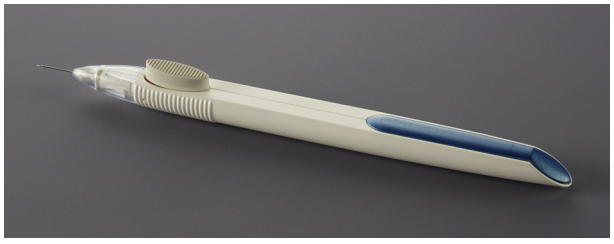


FIGURE 2. Bimatoprost sustained-release implant applicator system.

administered to achieve the 20-µg dose strength. Patients were masked to the dose strength of Bimatoprost SR received. After the injection, patients were provided with topical ophthalmic antibiotic solution to be instilled into the eye 4 times daily for the next 3 days. Patients were also dispensed bimatoprost 0.3% ophthalmic solution and were instructed to instill 1 drop in the fellow eye once daily in the evening for the duration of the study. Follow-up visits during the first year were scheduled on days 2 and 8; weeks 2, 4, 6, 8, 12, 16, and 20; and months 6, 7.5, 9, 10.5, and 12.

• **RESCUE AND RETREATMENT:** Rescue treatment using topical glaucoma drops could be initiated in either eye at the investigator's discretion if the eye failed to attain the target IOP (as determined by the investigator) on consecutive visits at least 1 week apart, or if it was considered to be in the best interest of the patient. After a protocol amendment, patients who received a ≤15-µg dose strength of Bimatoprost SR were eligible to receive a single repeat treatment with the same dose strength of the implant in the study eye between day 90 and month 12 if the following retreatment criteria were met: the patient had not received rescue therapy in either eye, the IOP at 8 AM in the study eye represented a <20% change from baseline IOP at consecutive visits at least 1 week apart, and the initial implant demonstrated adequate safety and did not contact the corneal endothelium. Retreatment could also be considered if, in the judgment of the investigator, there was a clinical indication for retreatment other than <20% IOP lowering (eg, visual field progression or optic disc hemorrhage). Retreatment with the 20-µg dose strength (2 10-µg implants) was not permitted because in this investigational study, which was the first study of the implant in humans, patients were allowed to receive no more than a total of 2 implants.

• **ASSESSMENTS AND OUTCOME MEASURES:** IOP was measured by Goldmann applanation tonometry at 8 AM at baseline and all follow-up visits. At selected study visits, additional measurements were taken at 10 AM, 12 PM, 2 PM, and 4 PM. At each time point, examiners masked to the treatment assignment took 2 or 3 IOP measurements for each eye using a 2-person, masked reading method.[17] The primary efficacy outcome measure was time-matched IOP change from baseline.

Other key outcome measures included use of rescue topical medication or implant retreatment. At a particular visit, a patient was considered to have been rescued or retreated if rescue medication or retreatment was received prior to the IOP measurement at that visit. The main safety

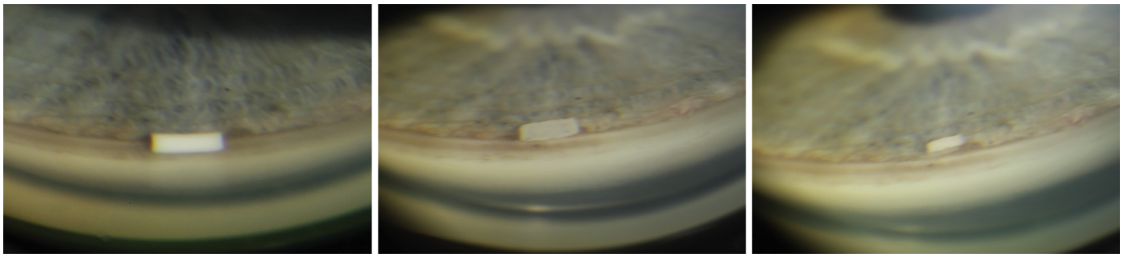


FIGURE 3. Gonioscopic photographs of bimatoprost sustained-release implant 10 μg in the anterior chamber of an eye of a representative patient diagnosed with open-angle glaucoma at (Left) 2 weeks, (Center) 9 months, and (Right) 12 months after injection.

measure was adverse events. Reports of adverse events included their seriousness, severity, and relationship to study treatment, as well as their duration and any action taken. Other safety evaluations included biomicroscopy (including assessment of lens opacities), ophthalmoscopy, macroscopic conjunctival hyperemia, iris color, gonioscopy (including residual implant assessments), visual acuity, visual fields, central corneal endothelial cell density by specular microscopy, corneal thickness by pachymetry, and OCT of the macula (week 4, week 12, and month 6) to monitor for the occurrence of cystoid macular edema.

A questionnaire was administered to patients on day 8 and week 4 after each injection asking whether the procedure in the study eye was much less burdensome, somewhat less burdensome, as burdensome, somewhat more burdensome, or much more burdensome than expected. An additional questionnaire administered at week 12 and month 24 (or early exit) asked patients how likely they would be to have the procedure again if given the choice, and how likely they were to recommend the procedure to someone else with their eye condition. Possible responses were extremely likely, very likely, somewhat unlikely, very unlikely, and extremely unlikely.

• **STATISTICAL ANALYSIS:** Analysis of efficacy and safety data through month 6 was performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina, USA). IOP was analyzed for the modified intent-to-treat population of all randomized patients with IOP data available for at least 1 time point at baseline and at least 1 time point during follow-up through week 16. The analysis of IOP used observed values, with IOP data collected after use of rescue medication or Bimatoprost SR retreatment censored from analysis. Time-matched changes in IOP from baseline were analyzed with 1-sample *t* tests comparing the mean change to 0. Differences in IOP lowering between study and fellow eyes were analyzed with paired *t* tests. The overall mean change from baseline IOP during the first 16 weeks of the study was calculated using all observations weighted equally and analyzed with 1-sample *t* tests comparing the overall mean change to 0. Adverse events were coded using Medical Dictionary for Regulatory Activities preferred terms and analyzed for the safety population of all patients who received implant. The occurrence of ocular adverse events typically associated with topical PGA use, including conjunctival hyperemia, eyelash growth, and iris pigmentation,[18] and less common but clinically relevant adverse events that have also been associated with topical PGA use, including periorbital pigmentation, blepharitis, eyelid erythema, eyelid edema, and periorbital fat atrophy,[18,19] were also evaluated.

The sample size was determined by a Data Review Committee, which reviewed the available efficacy and safety data during the course of the study and determined the doses of Bimatoprost SR to be evaluated, as well as the number of patients to be enrolled for each dose. The sample size was determined empirically rather than selected to provide power for statistical comparisons between implant dose strengths or between study and fellow eyes.

RESULTS

A TOTAL OF 75 PATIENTS WERE ENROLLED AT 24 SITES IN 6 countries (Australia, Canada, Israel, Philippines, Singapore, and the United States) and assigned to treatment with a 6-μg, 10-μg, 15-μg, or 20-μg dose strength Bimatoprost SR in the study eye and daily topical bimatoprost 0.03% in the fellow eye. After intracameral injection, implant could be visualized in the inferior iridocorneal angle, where it slowly eluted drug and biodegraded (Figure 3). For each dose strength of Bimatoprost SR, in the majority of study eyes the estimated size of residual implant at month 6 on gonioscopic examination was 75%–125% of the original size at injection, because the implant swells as it degrades. Upon goniscopy, the implant was generally observed to remain in the inferior angle of the eye in close proximity to the 6 o'clock position, with small changes in position noted from visit to visit. There were no adverse event reports related to patient complaints of floaters that would suggest implant movement during the typical day. All 75 patients received the study treatment and were included in the safety and efficacy analyses.

Baseline patient characteristics are listed in Table 1. The mean age was 63.2 years, and almost all patients

TABLE 1. Baseline Characteristics of Patients

Characteristic	BimSR 6 μg (N = 18)	BimSR 10 μg (N = 21)	BimSR 15 μg (N = 21)	BimSR 20 μg (N = 15)
Mean age, y (standard deviation)	60.4 (11.3)	65.4 (6.6)	63.2 (14.5)	63.5 (13.8)
Range	27–76	52–77	21–83	34–82
Sex, n (%)				
Male	6 (33.3)	12 (57.1)	11 (52.4)	8 (53.3)
Female	12 (66.7)	9 (42.9)	10 (47.6)	7 (46.7)
Race/ethnicity, n (%)				
White	10 (55.6)	15 (71.4)	17 (81.0)	11 (73.3)
Black or African-American	3 (16.7)	4 (19.0)	2 (9.5)	3 (20.0)
Asian	2 (11.1)	1 (4.8)	2 (9.5)	1 (6.7)
Hispanic	2 (11.1)	1 (4.8)	0	0
American Indian	1 (5.6)	0	0	0
Iris color, n (%)				
Dark (brown or dark brown)	13 (72.2)	10 (47.6)	10 (47.6)	7 (46.7)
Light (any other color)	5 (27.8)	11 (52.4)	11 (52.4)	8 (53.3)
Ocular diagnosis, n (%)				
Open-angle glaucoma (both eyes)	17 (94.4)	21 (100)	21 (100)	15 (100)
Open-angle glaucoma in study eye/ ocular hypertension in fellow eye	1 (5.6)	0	0	0
Number of topical glaucoma medications used concurrently in study eye before washout, mean (range)	1.3 (1–3)	1.1 (1–3)	1.2 (1–3)	1.4 (1–3)
Lens status in the study eye/fellow eye of each patient, n (%)				
Phakic/phakic	14 (77.8)	14 (66.7)	8 (38.1)	9 (60.0)
Pseudophakic/pseudophakic	4 (22.2)	7 (33.3)	13 (61.9)	6 (40.0)
Central corneal thickness, μm, mean (SD)[a]				
Study eyes	552 (44)	545 (66)	562 (39)	558 (42)
Fellow eyes	559 (38)	551 (61)	568 (38)	557 (47)
Central corneal endothelial cell density, cells/mm^2, mean (SD)				
Study eyes	2713 (256)	2671 (193)	2663 (181)	2718 (180)
Fellow eyes	2734 (236)	2623 (261)	2636 (191)	2709 (139)
IOP at 8 AM, mm Hg, mean (SD)				
Study eyes	25.1 (3.6)	24.5 (2.1)	25.1 (3.0)[b]	26.6 (4.1)[b]
Fellow eyes	24.4 (3.8)	24.1 (2.1)	24.2 (3.3)	25.5 (4.0)

BimSR = bimatoprost sustained-release implant; IOP = intraocular pressure; OAG = open-angle glaucoma; OHT = ocular hypertension; SD = standard deviation.

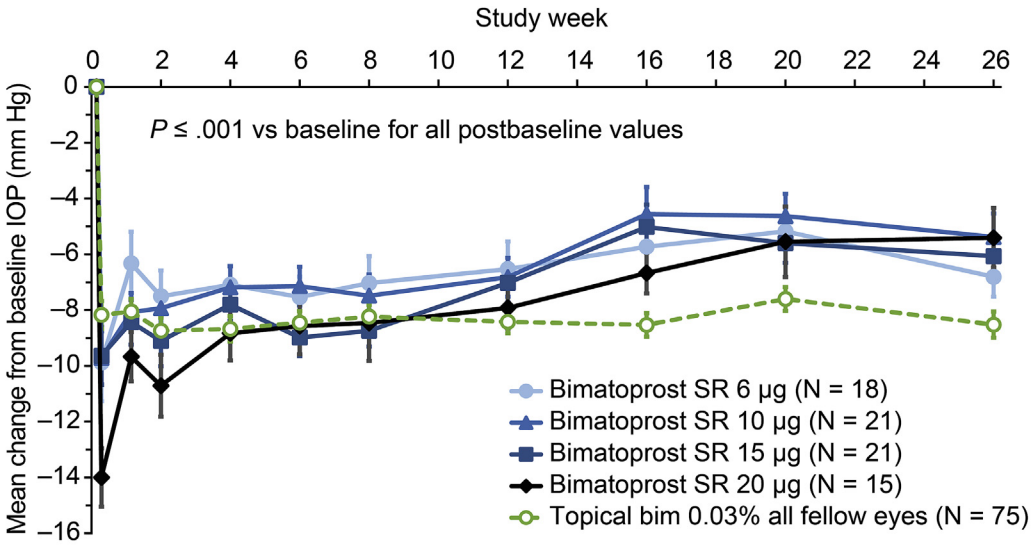
Study eyes were assigned to treatment with bimatoprost sustained-release implant; fellow eyes were assigned to treatment with once-daily topical bimatoprost 0.03%.

[a]Central corneal thickness was measured by noncontact pachymetry at the screening visit.

[b]$P \leq .009$ vs fellow eyes (paired *t* test).

(97.3%) were diagnosed with open-angle glaucoma in both eyes. The mean number of topical IOP-lowering medications used concurrently in the study eye prior to study enrollment was 1.2. Only 2 patients discontinued from the study before month 6 (a patient in the Bimatoprost SR 6-μg group, who had baseline diurnal IOP in the study eye ranging from 35 mm Hg at 8 AM to 46 mm Hg at 12 PM, discontinued on day 80, after receiving rescue topical medication in both eyes, for lack of efficacy, and a patient in the Bimatoprost SR 10-μg group, who had not required rescue, discontinued from the study on day 116 because the study site closed); 73 patients (97.3%) completed at least 6 months of follow-up.

• **EFFICACY OUTCOMES:** Bimatoprost SR provided rapid and sustained IOP lowering (Figure 4). Clinically and statistically significant ($P \leq .001$) decreases in IOP were observed in study eyes as early as 1 day after Bimatoprost SR administration and at all subsequent follow-up visits through month 6. During the first 12 weeks of the study,



BimSR not rescued or retreated, %	100	99	99	97	95	91	75	71
n at time points for each BimSR dose strength								
6 µg	17	16	17	17	17	15	14	13
10 µg	21	19	21	20	19	17	16	13
15 µg	20	20	20	21	21	21	15	14
20 µg	14	15	15	13	12	12	11	11
Topical bim 0.03% not rescued, %	100	100	100	97	97	97	97	97
n at time points for pooled fellow eyes treated with topical bim 0.03%								
Topical bim	72	71	74	71	71	69	72	70

FIGURE 4. Mean change from baseline intraocular pressure (IOP; 8 AM time point) in study eyes after bimatoprost sustained-release implant administration and in fellow eyes treated with once-daily topical bimatoprost 0.03%. The percentage of study eyes that had not received rescue topical IOP-lowering medication or implant retreatment and remained in the analysis is indicated, as is the percentage of fellow eyes that had not received rescue topical IOP-lowering medication and remained in the analysis. Bim = bimatoprost; BimSR and Bimatoprost SR = bimatoprost sustained-release implant. Error bars represent standard error of the mean.

a dose response was generally evident, and the IOP lowering with all dose strengths of the implant was in the range expected with a topical ophthalmic PGA (Figure 4). Overall, the 8 AM mean IOP reduction from baseline through week 16 in study eyes ranged from 7.2 to 9.5 mm Hg after a single administration of Bimatoprost SR and was similar to the reduction of 8.4 mm Hg seen in pooled fellow eyes receiving once-daily treatment with topical bimatoprost 0.03% (Table 2).

During the first 12 weeks of follow-up, the only statistically significant differences between study and fellow eyes in 8 AM mean reduction from baseline IOP were at day 2, when differences favored Bimatoprost SR for each dose strength of Bimatoprost SR ($P \leq .039$), and at week 12, when the difference favored topical bimatoprost in the Bimatoprost SR 6-µg group ($P = .042$). At subsequent visits through month 6, differences in IOP reductions between study eyes and fellow eyes favored topical bimatoprost and were sometimes statistically significant. The 8 AM mean IOP reduction from baseline in study eyes at month 6 ranged from 5.4 to 6.8 mm Hg in the Bimatoprost SR 6-µg, 10-µg, 15-µg, and 20-µg groups. Diurnal IOP changes from baseline at 10 AM, 12 PM, 2 PM, and 4 PM were consistent with the 8 AM results.

Rescue with topical IOP-lowering medication or implant retreatment was required by only 4 (4/75, 5.3%) study eyes up to week 12 and 6 (6/75, 8.0%) study eyes up to week 16 (Figure 4). At month 6, 71% of study eyes

TABLE 2. Average Intraocular Pressure Reductions Over 16 Weeks

Treatment	N	Mean Overall IOP Reduction From Baseline Through Week 16, mm Hg[a]	*P* Value
Bimatoprost SR 6 μg	18	7.2	<.001
Bimatoprost SR 10 μg	21	7.4	<.001
Bimatoprost SR 15 μg	21	8.1	<.001
Bimatoprost SR 20 μg	15	9.5	<.001
Topical bimatoprost 0.03% QD (pooled fellow eyes)	75	8.4	<.001

Bimatoprost SR = bimatoprost sustained-release implant; IOP = intraocular pressure; QD = once daily.

[a]Overall IOP reduction was calculated using IOP reduction from baseline values from day 2 through week 16; these values were averaged with all values weighted equally and data censored at rescue or retreatment.

still had not received topical IOP-lowering rescue medication or a second injection of Bimatoprost SR and remained in the analysis (Figure 4).

• **SAFETY OUTCOMES:** One or more ocular adverse events were reported in the study eye of 39 of 75 patients (52.0%) and in the fellow eye of 23 patients (30.7%). The most common adverse events in study eyes were conjunctival hyperemia, foreign body sensation, eye pain, increased lacrimation, conjunctival hemorrhage, and punctate keratitis (Table 3). The overall incidence of ocular adverse events was higher in eyes treated with Bimatoprost SR because of adverse events that occurred within 2 days after intracameral injection, resolved quickly, and were likely related to the injection procedure, including conjunctival hyperemia, foreign body sensation, eye pain, increased lacrimation, and conjunctival hemorrhage.

Conjunctival hyperemia was the most common ocular adverse event in both study eyes and fellow eyes (Table 3). In study eyes that had a report of conjunctival hyperemia within 2 days after the initial Bimatoprost SR administration, the median duration of hyperemia was 5 days, consistent with the premise that in most cases, early-onset hyperemia was related to the injection procedure. Five study eyes developed late-onset hyperemia at a median of 121 days (range, 85–175 days) postinjection. The late-onset hyperemia resolved a median of 46 days after onset in 4 of these eyes and is ongoing in 1 eye. Adverse events related to intraocular inflammation were reported in 4 study eyes, were temporally associated with the injection procedure, and resolved without sequelae after either topical corticosteroid treatment or no treatment. In 3 of the eyes, mild anterior chamber inflammation, cells, or flare was reported at 1–6 days after implant injection and resolved without treatment. In the fourth eye, moderate cyclitis was reported on day 2; it was treated with topical prednisolone and resolved in 6 days. There were 8 adverse event reports of blurred vision or reduced visual acuity in 7 study eyes (1 eye had 2 adverse event reports). Of these 8 adverse events, 6 occurred within 2 days after Bimatoprost SR administration, and 7 had resolved by month 6 (median time to resolution, 5 days; range, 1–12 days). Cataract was reported as an adverse event with onset at day 21 in 1 study eye. The patient had no adverse event report of any visual disturbance or any complication of the injection procedure. On biomicroscopy, nuclear cataract in this eye increased from +1 at baseline to +2 at month 6. Best-corrected visual acuity in the study eye was 78 letters at baseline and 73 letters at month 6. There were no reports of cystoid macular edema (by clinical examination or by OCT) or endophthalmitis in any study eye. Iris color change was reported in 1 fellow eye and no study eyes.

Among adverse events typically associated with topical PGA use, those with onset later than 2 days after Bimatoprost SR injection were more likely to be drug related and were more common in eyes treated with topical bimatoprost 0.03% than in eyes treated with Bimatoprost SR (Table 3). Notably, conjunctival hyperemia with onset later than 2 days after Bimatoprost SR injection was reported in only 5 of 75 (6.7%) study eyes compared with 13 of 75 (17.3%) fellow eyes, and eyelash growth was reported in no study eyes and 2 fellow eyes (Table 3). Although not reported as adverse events, 2 fellow eyes treated with topical bimatoprost and no study eyes were noted to have periorbital fat atrophy upon biomicroscopic examination.

The occurrence of adverse events was similar across the Bimatoprost SR dose strengths. There were no serious ocular adverse events in any study eyes, and no implants had to be removed for safety reasons. The only serious ocular adverse event reported (retinal detachment requiring surgical repair) occurred in a fellow eye treated with topical bimatoprost 0.03%. There were no systemic safety concerns.

In other safety evaluations through month 6, there were no significant differences between study eyes and fellow eyes from the continuous safety monitoring or the analysis of corneal endothelial cell density and corneal thickness. Mean (± standard deviation) central corneal endothelial cell density at month 6 was 2638 ± 206 cells/mm^2 in study eyes and 2650 ± 222 cells/mm^2 in fellow eyes; mean (± standard deviation) central corneal thickness at month 6 was 557 ± 43 μm in study eyes and 555 ± 45 μm in fellow eyes.

• **PATIENT-REPORTED OUTCOMES:** At day 8, the Bimatoprost SR procedure was reported to be less burdensome than expected by 79.7% (59/74) of patients (Table 4). At week 12, 77.8% (56/72) of patients reported that they were very or extremely likely to have another implant

TABLE 3. Ocular Adverse Events Reported in At Least 2 Study or Fellow Eyes During the First 6 Months of the Study

	Onset Any Time		Onset >2 Days After BimSR Injection or Repeat Injection	
	No. of Patients (%)		No. of Patients (%)	
Adverse Event	Study Eyes BimSR (N = 75)	Fellow Eyes Bim 0.03% (N = 75)	Study Eyes BimSR (N = 75)	Fellow Eyes Bim 0.03% (N = 75)
Conjunctival hyperemia[a]	18 (24.0)	14 (18.7)	5 (6.7)	13 (17.3)
Foreign body sensation in eye	12 (16.0)	0	1 (1.3)	0
Eye pain	10 (13.3)	0	0	0
Lacrimation increased	10 (13.3)	0	0	0
Conjunctival hemorrhage	9 (12.0)	0	2 (2.7)	0
Punctate keratitis	7 (9.3)	2 (2.7)	3 (4.0)	2 (2.7)
Intraocular pressure increased	6 (8.0)	2 (2.7)	6 (8.0)	2 (2.7)
Photophobia	6 (8.0)	2 (2.7)	3 (4.0)	2 (2.7)
Vision blurred	5 (6.7)	1 (1.3)	2 (2.7)	1 (1.3)
Visual acuity reduced	3 (4.0)	2 (2.7)	0	1 (1.3)
Eye irritation	3 (4.0)	0	0	0
Corneal abrasion	2 (2.7)	0	0	0
Eyelid erythema[a]	1 (1.3)	2 (2.7)	1 (1.3)	2 (2.7)
Growth of eyelashes[a]	0	2 (2.7)	0	2 (2.7)
Overall[b]	39 (52.0)	23 (30.7)	24 (32.0)	22 (29.3)

Bim = bimatoprost; BimSR = bimatoprost sustained-release implant.

[a]Adverse event typically associated with use of a topical prostaglandin analog.

[b]Patients with any ocular adverse event reported over 6 months with any time of onset or onset later than 2 days after injection or repeat injection of BimSR.

procedure, and 83.3% (60/72) of patients were very or extremely likely to recommend the implant (Table 4).

DISCUSSION

THIS IS THE FIRST REPORT OF THE IOP-LOWERING EFFICACY and safety of an intracameral bimatoprost-eluting implant in patients with glaucoma. The 6-month study results show that Bimatoprost SR was well tolerated and effectively reduced IOP. Through week 16, >90% of study eyes had not been rescued or retreated and remained in the IOP analysis, and all dose strengths of Bimatoprost SR were comparable with topical bimatoprost in overall IOP reduction. In most patients, a single administration of Bimatoprost SR controlled IOP without need for rescue topical medication or implant retreatment for up to 6 months. The implant was designed to release bimatoprost to lower IOP for 4–6 months, so we expected and observed that a higher proportion of study eyes required rescue at 6 months than at 16 weeks. The majority of ocular adverse events occurred within 2 days of Bimatoprost SR administration, in association with the intracameral injection procedure, and were transient. Furthermore, most patients were highly satisfied with Bimatoprost SR treatment and found it less burdensome than expected.

The total dose of bimatoprost contained in the Bimatoprost SR 10-μg implant is similar to the dose in a single drop of ophthalmic bimatoprost 0.03% solution. Thus, total drug exposure was much less in eyes that received implant compared with eyes that received daily topical treatment. Reduced total drug exposure, along with the close proximity of implant to the target tissues (the trabecular meshwork and ciliary body), may be expected to improve the safety profile of bimatoprost treatment. In a preclinical study in dogs, drug delivery was targeted to the iris–ciliary body after Bimatoprost SR administration, and drug concentrations in the bulbar conjunctiva, eyelid margin, and periorbital fat were remarkably reduced or undetectable with the implant compared with topical bimatoprost administration (Seal JR, et al. Ocular distribution of bimatoprost following intracameral administration of a 15-μg sustained-release bimatoprost implant or topical administration of bimatoprost 0.03%. Paper presented at the Asia-Pacific Academy of Ophthalmology Congress. March 24, 2016; Taipei, Taiwan). Consistent with these findings, in the 6-month clinical study results, there were no cases of periocular skin discoloration, periorbital fat atrophy, or eyelash growth in eyes injected with Bimatoprost SR, and PGA-associated adverse events with onset later than 2 days after the injection procedure were less frequent in study eyes than in fellow eyes treated with topical bimatoprost. Pharmacokinetic data on the ocular distribution of bimatoprost in humans after administration of Bimatoprost SR are unavailable. However, the results are consistent with the premise that use of a sustained-release intracameral implant can more selectively deliver

TABLE 4. Bimatoprost Sustained-Release Implant for Glaucoma Treatment: Patient-Reported Outcomes

Response to Questionnaire	No. of Patients (%)	
Day 8 and Week 4: Was the procedure in the study eye as burdensome as you expected? (N = 74)	Day 8	Week 4
Much less burdensome than I thought it would be	47 (63.5)	42 (56.8)
Somewhat less burdensome than I thought it would be	12 (16.2)	16 (21.6)
As burdensome as I thought it would be	9 (12.2)	13 (17.6)
Somewhat more burdensome than I thought it would be	4 (5.4)	3 (4.1)
Much more burdensome than I thought it would be	2 (2.7)	0 (0)
Week 12: If given the choice again, are you likely to have the implant procedure? (N = 72)		
Extremely likely	40 (55.6)	
Very likely	16 (22.2)	
Somewhat unlikely	7 (9.7)	
Very unlikely	3 (4.2)	
Extremely unlikely	6 (8.3)	
Week 12: Are you likely to recommend the implant to someone else with your eye condition? (N = 72)		
Extremely likely	43 (59.7)	
Very likely	17 (23.6)	
Somewhat unlikely	6 (8.3)	
Very unlikely	2 (2.8)	
Extremely unlikely	4 (5.6)	

bimatoprost to target tissues and lead to fewer adverse effects caused by drug exposure to the ocular surface and surrounding tissues. There were no serious adverse events in study eyes, and adverse events related to the intracameral injection procedure were expected and resolved without sequelae. Other than conjunctival hemorrhage, which was generally associated with toothed forceps fixation of the eye before injection, many of these early-onset adverse events were attributed by investigators to the use of povidone-iodine irrigation, which is standard of care to prevent infection during intraocular injections. Ocular instillation of a povidone-iodine solution in human subjects has been shown to have effects on both visual acuity and the ocular surface and to cause subjective symptoms in the 24 hours postinstillation (Oquindo C, et al. IOVS 2016;57: ARVO E-Abstract 3854). Many adverse events occurring in the first 24 hours after implant treatment were topical, suggesting that they were likely related to the povidone-iodine irrigation. However, non-zero-order kinetics of drug release and a high drug concentration immediately after implant injection potentially could also result in early-onset adverse events. Although there is currently no evidence of non-zero-order kinetic release with the implant, this possibility cannot be completely ruled out.

Interim analyses are inherent to adaptive trial designs,[20] and we performed the present analysis on 6-month data as part of the adaptive process to accelerate decisions regarding further development of the implant. Analysis of the 6-month data provided useful information on the differentiation between dose strengths and the duration of effect. The long-term safety of 1 or 2 implants over 2 years of follow-up will be reported when the study is completed.

Bimatoprost 0.03% ophthalmic solution was used as the active comparator because at the initiation of the study, the bimatoprost 0.03% formulation was in use in all of the countries with participating sites. The efficacy observed in the topical treatment arm was consistent with the 30%–35% IOP lowering typically reported in studies of topical bimatoprost 0.03%.[21] A bimatoprost 0.01% formulation that demonstrates the same efficacy and improved tolerability[22,23] is now the only topical ophthalmic formulation of bimatoprost available for use in the United States.

In this study, the effects of Bimatoprost SR were evaluated in a population of patients who had mild to moderate visual field loss and who had demonstrated previous response to topical PGAs. Therefore, the results are not necessarily generalizable to patients with more advanced disease or on maximum tolerated medical therapy, or who have not had prior experience with a PGA. In addition, the ocular tolerability observed in fellow eyes treated with topical bimatoprost in this study may have been affected both by the selection of patients with no greater than mild conjunctival hyperemia after previous topical PGA treatment (resulting in better apparent tolerability) and by use of bimatoprost 0.03% rather than bimatoprost 0.01% (resulting in worse apparent tolerability). No implants had to be removed for safety reasons. It will be important to monitor any need for implant removal in follow-up studies. Long-term data on protection of visual function with the implant are also needed, and visual fields will be monitored in future studies.

Medication adherence is a critical public health issue for individuals and health care systems in the United States and worldwide.[24] It has been estimated that poor adherence results in $100–$300 billion in health care costs in the United States each year, or 3%–10% of total health care spending.[4] Recent initiatives to improve adherence include a campaign of the National Consumers League assembling stakeholders in health care, business, and government to raise awareness about the importance of medication adherence in all chronic diseases.[25] Clinical studies have suggested that adherence to glaucoma medication is critical for optimal visual outcomes.[10,11] Poor glaucoma medication adherence was also associated with visual field progression in a recent large pharmacy and medical claims–based study (Fong D. Poor medication adherence increases visual field progression in glaucoma. Paper presented at the AAO Annual Meeting. November 16, 2015; Las Vegas, Nevada).

The potential for improved patient adherence to treatment with long-acting injections is recognized in other therapeutic areas. For example, the antipsychotic medication risperidone has long been used for treatment of schizophrenia. Formulations that provide sustained release of the drug from polylactic-co-glycolic acid microspheres or paliperidone nanoparticles allow dosing with a long-acting injection every 2 or 4 weeks, respectively, rather than a daily oral dose. Long-acting injectable risperidone is at least as effective as oral dosing and is preferred for patients with poor adherence.[26]

In ophthalmology, an intravitreal implant employing the biodegradable NOVADUR platform used with Bimatoprost SR provides sustained release of dexamethasone and is approved by the US Food and Drug Administration for treatment of macular edema related to retinal vein occlusion, noninfectious posterior segment uveitis, and diabetic macular edema.[27] The implant contains micronized dexamethasone in a polylactic-co-glycolic acid copolymer matrix and has been on the market since 2009. The matrix slowly degrades to lactic acid and glycolic acid through hydrolysis, releasing dexamethasone into the vitreous for up to 6 months.[28] Reducing the number of intravitreal injections required to treat retinal diseases is helpful to reduce the treatment burden on patients and may improve the overall quality of life.

The NOVADUR platform can be modified to provide different release profiles. The dexamethasone implant was formulated to provide a pulse of dexamethasone release followed by maintenance release,[28] as pulse therapy with corticosteroid is preferred in severe inflammatory disease of the posterior segment.[29] For glaucoma treatment, nonpulsatile, steady-state drug release (ie, zero-order kinetics) over time is desirable, and the NOVADUR platform in Bimatoprost SR was modified to provide this drug release profile.

In summary, Bimatoprost SR may represent a transformational approach to address the endemic problem of nonadherence to topical glaucoma medication. The miniaturized drug delivery platform also may be applicable to treatment of other chronic diseases of the eye. Interim safety and efficacy results from this study are favorable and suggest that Bimatoprost SR has the potential to improve patient adherence to therapy, which may ultimately lead to improved treatment outcomes in glaucoma. The results support further clinical development of the implant.

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