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ORIGINAL RESEARCH ARTICLE

Prospective 18-Month Study of Bimatoprost Intracameral Implant in Patients with Open-Angle Glaucoma or Ocular Hypertension in US Clinical Practice

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Abstract

Background and Objective Bimatoprost implant 10 µg (Durysta) is an intracameral biodegradable implant that releases bimatoprost to lower intraocular pressure (IOP). The purpose of this study was to prospectively collect effectiveness and safety data after administration of the implant in patients with open-angle glaucoma or ocular hypertension.

Methods This phase IV, multicenter, prospective, observational, open-label, 18-month study (ARGOS) enrolled adult patients with open-angle glaucoma or ocular hypertension who were scheduled to receive the bimatoprost implant in one or both eyes. Data collected included IOP, use of topical IOP-lowering medications, treatment-emergent adverse events, and central corneal endothelial cell density. The primary endpoint was the proportion of primary (first-treated) eyes that received no additional (new) IOP-lowering treatment per standard medical care through month 6 after the implant administration.

Results A total of 217 patients (341 eyes) were enrolled, and 132 patients (60.8%) and 203 eyes (59.5%) completed the study. Most patients were on topical IOP-lowering medication before receiving the implant. After implant administration, the proportion of primary eyes that had received no additional treatment was 88.6% (95% confidence interval 86.6–90.6) at month 6 (primary endpoint) and remained high throughout the follow-up: 83.7% (95% confidence interval 80.2–87.3) at month 12 and 77.7% (95% confidence interval 73.4–82.1) at month 18. Intraocular pressure was reduced after implant administration, with mean changes in IOP from baseline at follow-up visits ranging from − 1.0 to − 2.0 mm Hg. The mean number of topical IOP-lowering medications used was also reduced, from 1.8 at baseline to 0.9 at month 12 and 1.0 at month 18. Increased IOP and dry eye were the most common ocular treatment-emergent adverse events. The mean percentage change in central corneal endothelial cell density from baseline at month 18 (central reading center evaluation) was − 3.47%. In qualitative interviews, most patients (84%, 21/25) reported overall satisfaction with their treatment outcomes.

Conclusions The bimatoprost implant helped control IOP and decrease topical medication use. Throughout the 18 months after implant administration, an estimated 77.7% of eyes required no new added medication for IOP management. Patient-reported outcomes were favorable, and the safety profile of the implant was acceptable.

Clinical Trial Registration ClinicalTrials.gov identifier NCT04647214, registered 23 November, 2020.

1 Introduction

Open-angle glaucoma (OAG) is a chronic progressive vision-threating disease and a leading cause of irreversible blindness [1]. The global prevalence of primary OAG in individuals aged 40–80 years was estimated to be 53 million in 2020 and is projected to be 80 million in 2040 [2]. All currently approved treatments for OAG aim to reduce intraocular pressure (IOP). Lowering IOP has been proven to slow the progression of visual field loss in patients with glaucoma [3, 4] and reduce the risk of development of glaucoma in individuals with ocular hypertension (OHT) [5]. Treatment options to lower IOP include topical medications, intraocular implants, laser procedures, and incisional surgeries.

Initial treatment in OAG and OHT is typically topical medications (eye drops) [6, 7]. Prostaglandin analog/prostamide (PGA), beta-blocker, alpha-adrenergic agonist, carbonic anhydrase inhibitor, rho kinase inhibitor, and

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Key Points

Most eyes treated with the bimatoprost implant needed no additional (new) intraocular pressure–lowering treatment for up to 18 months after the implant administration.

On average, after the bimatoprost implant was administered, both intraocular pressure and topical medication burden were reduced compared with pre-implant levels.

The safety profile of the bimatoprost implant over the 18-month study was acceptable.

cholinergic agonist medications are available in topical ophthalmic formulations for lowering IOP [8]. The eye drops usually are prescribed for once- or twice-daily use. Each drop contains a single medication or a fixed combination of two medications, and patients can be prescribed multiple different drops for concomitant use.

Poor adherence of patients to topical IOP-lowering medications is a frequent and well-recognized problem in glaucoma management [9, 10]. Studies generally have shown that 30–80% of patients do not use their IOP-lowering medications as prescribed [11–13] and have further shown that poor adherence is associated with worse visual field progression [14, 15]. Many reasons for poor adherence to IOP-lowering eye drops have been identified, such as memory problems/forgetting to use the drops, difficulties in instilling a drop in the eye because of a disability (such as arthritis, tremor, or weakness of the hands; poor vision; or difficulty in tilting the head back), the inconvenience of having to use multiple drops and/or dose multiple times each day, side effects, medication costs, and a lack of understanding of the importance of consistent use of the drops to reduce the risk of visual field loss [16–22]. It is important to identify nonadherent patients and consider alternative approaches to therapy for patients who are unable to adhere to eye drops [23]. Strategies of care not requiring patient adherence that may potentially be useful as an alternative to eye drops include laser trabeculoplasty, drainage devices implanted with minimally invasive glaucoma surgery, and intraocular devices that provide sustained release of IOP-lowering medication [24]. It has been suggested that the presence of comorbidities should be considered, as neurodegenerative disease affecting cognition and memory, motor disease, and low vision are common in patients with glaucoma and may limit adherence to eye drops [25]. Patients with these comorbidities may benefit from a non-drop treatment modality [25].

A biodegradable sustained-release bimatoprost implant (Durysta; AbbVie, North Chicago, IL, USA) was developed to address the problem of nonadherence to topical IOP-lowering medications in glaucoma [26]. The small rod-shaped implant (diameter ~200 µm, length ~1.1 mm) consists of 10 µg of the PGA bimatoprost in a poly-lactic acid/polylactic-co-glycolic polymer matrix [27]. The implant is administered with a single-use, prefilled, 28-gauge applicator into the anterior chamber, where it provides continuous drug release for several months [27]. The polymer matrix is gradually metabolized and hydrolyzed to carbon dioxide and water [28]. Bimatoprost implant 10 µg is approved in the USA for single use per eye to lower IOP in OAG and OHT [29].

Data on the duration of the IOP-lowering effect and safety of a single bimatoprost implant are limited because the large registration trials of the implant used multiple implant administrations. In a phase I/II study, 21 patients with OAG received a single administration of bimatoprost implant 10 µg in the study eye [26, 30]. The implant effectively reduced IOP and was well tolerated, and five patients (23.8%) needed no additional IOP-lowering treatment for up to 2 years [30]. In the ARTEMIS phase III clinical trials comparing the bimatoprost implant with topical timolol in patients with OAG and OHT, a single bimatoprost implant lowered IOP similarly to twice-daily topical timolol treatment through 15 weeks and had an acceptable safety profile [27, 29, 31]. Because the study design included repeat dosing of the bimatoprost implant at weeks 16 and 32, it was not possible to evaluate the effects of a single implant at later timepoints in the ARTEMIS trials. Corneal endothelial cell loss (ECL) was a clinical concern in some eyes that had received multiple implant administrations [27, 29]. In a phase IIIb study evaluating 24-hour IOP lowering after a single administration of the bimatoprost implant in patients with OAG or OHT, 23 of 31 patients (74.2%) needed no additional IOP-lowering treatment in the study eye for 12 months [32]. The most common adverse event reported in each of these prospective clinical studies was conjunctival hyperemia associated with the administration procedure [27, 29, 30, 32].

Studies of the use and effectiveness and safety outcomes of the bimatoprost implant in the real world are necessary to inform clinical practice. Four retrospective single-site case series have been reported, each showing a sustained duration of effectiveness of the bimatoprost implant [33–36]. The purpose of the present study was to prospectively collect effectiveness and safety data after administration of a bimatoprost implant in patients with OAG or OHT. The decision to treat patients was made by the investigator prior to and independent of patients' enrollment in the study. Follow-up during the study reflected standard care with the addition of specular microscopy to evaluate potential ECL.

2 Methods

2.1 Study Design and Ethical Conduct

This prospective, observational, open-label, multicenter (32 sites in the USA), cohort study (ARGOS) evaluated outcomes of bimatoprost implant treatment in patients with OAG or OHT who were scheduled for bimatoprost implant administration in one or both eyes. The planned study duration was 18 months for each implant-treated eye. The first patient study visit was on 3 March, 2021, and the study was completed on 12 July, 2024. The study was conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. An institutional review board or independent ethics committee approved the study protocol, informed consent forms, and recruitment materials at each site before patient enrollment, and all patients provided written informed consent before screening. The study is registered at ClinicalTrials.gov with the identifier NCT04647214.

2.2 Study Population

The study enrolled adult patients (aged ≥ 18 years) diagnosed with OAG or OHT who were scheduled to receive a bimatoprost intracameral implant in at least one eye. Investigators were asked to refer to the bimatoprost implant prescribing information for information on contraindications, warnings and precautions, and use of the implant in specific populations. The decision to treat the patient with the bimatoprost implant had to be made prior to and independent of the decision to include the patient in the study. Central corneal endothelial cell density (CECD) measured on specular microscopy in the eye(s) to be treated with the bimatoprost implant was required to be ≥ 2000 cells/mm^2.

Under the initial study protocol, the eye scheduled for bimatoprost implant treatment was required to have no history of implantation of an Ahmed glaucoma valve, Baerveldt shunt, Ex-Press glaucoma shunt, Molteno shunt, or CyPass micro-stent, as well as no history of trabeculectomy, vitrectomy, retinal surgery, or anterior chamber intraocular lens placement. After a protocol amendment in December 2021, the list of exclusion criteria was expanded, and the eye scheduled for bimatoprost implant treatment was required to have no history of: (1) laser procedures (trabeculoplasty within the past 24 months or ciliary ablation); (2) angle procedures (trabecular bypass within the past 24 months, or trabecular extirpation, canal dilation, or suprachoroidal shunt or bypass); and (3) filtering procedures or shunts/bypass (sclerotomy, deep sclerectomy, trabeculectomy, bypass device with ab-interno or ab-externo placement, or device with plate or reservoir). Patients who had previously enrolled in another bimatoprost implant study, or who were enrolled or planned enrollment in an interventional clinical trial involving an investigational medical product or device, were excluded.

If both eyes from the same patient met the eligibility criteria, both eyes could be enrolled, with the patient providing consent separately for each eye. The eye that was scheduled to be treated first was selected as the primary study eye and included in the effectiveness analyses. If both eyes were scheduled to be treated at the same time, the right eye was selected as the primary eye.

2.3 Enrollment and Patient Care During Study

Patients and eyes meeting all eligibility criteria during screening were enrolled in the study by the investigator, who assigned a target IOP to each eligible eye before its enrollment and the administration of the bimatoprost implant. Treatments, diagnostic procedures, and follow-up schedules during the study were at the discretion of the investigators according to their clinical judgment and the local standard of care, except for specular microscopy (which is not standard of care) and patient-reported outcomes. Investigators were asked to perform specular microscopy on the central cornea at approximately 6-month intervals after administration of the bimatoprost implant, until the end of the follow-up at 18 months after the implant administration for each treated eye. All investigative sites received training on correct performance of the specular microscopy. For each enrolled eye, autocounts of CECD were recorded by the investigator, and specular microscopy images from the screening, follow-up, and end-of-study visits were sent to a central reading center (CRC) for assessment. During the follow-up period after implant administration, additional IOP-lowering treatment (medical or surgical) was used per standard medical care.

2.4 Data Collection

Investigators recorded baseline data in the period leading up to and including the date of administration of the bimatoprost implant. The baseline data collected included demographics and medical history, and for each enrolled eye, ophthalmic history, gonioscopic angle assessment, the target IOP, and the reason for using the bimatoprost implant. Details of the implant administration procedure (e.g., the type of facility used for the procedure, and the use of topical antibiotic before and after the administration) were also recorded.

Other available data recorded for each enrolled eye at baseline (prior to the implant administration), follow-up visits during the study, and the final study visit (at approximately month 18) included IOP, concomitant medications

and procedures for IOP control, adverse events, CECD autocounts, findings on biomicroscopy, ophthalmoscopy, and optic disc examination, central corneal thickness (by pachymetry), best-corrected visual acuity (BCVA), and visual fields. Assessments of implant size and location were also recorded at follow-up visits and the final study visit.

If an implant-treated eye underwent implant removal or intraocular (incisional) surgery, or the investigator determined that the IOP was not at target and required additional IOP-lowering treatment, the eye was switched to follow-up for safety parameters only. The investigator had the option to continue to record IOP and IOP-lowering medication use after the eye was switched to safety follow-up.

2.5 Outcome Measures

The primary effectiveness endpoint was the proportion of implant-treated eyes that received no additional IOP-lowering treatment per standard medical care through month 6 after the implant administration. Additional IOP-lowering treatment was defined as any new medical, laser, or surgical IOP-lowering therapy, an increase in the dose or dosing frequency of an ongoing topical IOP-lowering medication, or replacement of one ongoing IOP-lowering medication by another.

Secondary effectiveness endpoints included the proportion of implant-treated eyes receiving no additional IOP-lowering treatment per standard medical care through month 4 (key secondary endpoint) and months 9, 12, and 18 after the implant administration; the time from the bimatoprost implant administration to the first additional IOP-lowering treatment; and the mean reduction from baseline in the number of topical IOP-lowering medications used at months 4, 6, 9, 12, and 18. In addition, the observed IOP at baseline and months 4, 6, 9, 12, and 18 was a preplanned exploratory effectiveness endpoint. Key safety endpoints included CECD and the incidence of ocular adverse events.

Patient-reported outcomes secondary endpoints included the acceptability of the bimatoprost implant procedure as well as results of the Glaucoma Quality of Life 15-item (GQL-15) questionnaire [37] and semi-structured patient interviews regarding their disease experience and treatment journey. In the initial study protocol, patients were asked about the burdensomeness of the implant procedure at their first follow-up visit after a bimatoprost implant administration, rating it on a 5-point scale from "much more burdensome than expected" to "much less burdensome than expected." Subsequently, patients who enrolled after the study protocol amendment were administered the GQL-15 questionnaire at baseline and the final visit. The GQL-15 questionnaire consists of 15 items covering four dimensions of central and near vision (two items), peripheral vision (six items), dark adaptation and glare (six items), and outdoor mobility (one item), with responses on a 5-point scale from 1 (no difficulty) to 5 (severe difficulty). A subset of enrolled patients participated in patient interviews, which were optional. The 1-hour interviews were conducted via videoconference at 4–6 months after implant administration and focused on treatment experience, tolerability, effectiveness, and satisfaction.

2.6 Data Analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). The enrolled population consisted of all patients who signed the informed consent form, had at least one eye that was not a screen failure, and had no major protocol deviations related to exclusion criteria. Patient baseline characteristics were analyzed in the full analysis set (FAS) of patients, defined as all enrolled patients who received a bimatoprost implant in the primary (first treated) eye and had at least one post-administration assessment. Analyses of effectiveness and baseline ocular characteristics used the FAS of eyes, defined as all enrolled primary eyes that received the bimatoprost implant and had a post-administration assessment available. Safety parameters were evaluated in all enrolled patients and eyes that received the bimatoprost implant.

The preplanned timepoints of interest were 4, 6, 9, 12, and 18 months after the day 1 administration of the bimatoprost implant. Collected data were analyzed using the visit windows of days 2–150 (month 4), days 150–225 (month 6), days 226–315 (month 9), days 316–450 (month 12), and days 451 to the end of the study (month 18). If multiple visits occurred within a visit window, data collected at the visit nearest in time to the nominal visit day (day 120 for month 4, day 180 for month 6, day 270 for month 9, day 360 for month 12, and day 540 for month 18) were used for analysis. For each implant-treated eye, the baseline values used for analysis were the last assessments available before the implant administration.

The number of topical IOP-lowering medications at baseline was defined as the number used prior to the implantation. Medications were counted by class, i.e., a fixed combination was counted as two medications. For follow-up timepoints, the medication count included all medications used at any time on or after the date of the previous visit, i.e., the month 4 count included all medications used at any time on or after the implant administration visit, the month 6 count included all medications used at any time on or after month 4 visit, and the month 9 count included all medications used at any time on or after month 6 visit. If an eye had no visit within a specific visit window but remained in the study, medication use and counts for the specific visit were determined based on medication use and medication start/stop dates recorded at a later visit.

In the primary analysis of the proportion of eyes in the FAS with no additional IOP-lowering treatment at month 6 (primary endpoint) and months 4, 9, 12, and 18, for eyes that were lost to follow-up or discontinued from the study before receiving additional IOP-lowering treatment, multiple imputation was applied for missing data after the loss to follow-up or study discontinuation. A logistic regression model with age, sex, baseline lens status, number of IOP-lowering medications at baseline, baseline IOP, and baseline visual field mean deviation as covariates was used to predict individual probability in each imputation dataset. Percentages and 95% confidence intervals (CIs) were computed by calculating the mean and standard deviation (SD) of the predicated probabilities.

Sensitivity analysis of the primary endpoint and all other effectiveness analysis used observed values in the FAS. Safety analyses used all available data for all enrolled eyes that received the bimatoprost implant. Adverse events were coded using *Medical Dictionary for Regulatory Activities* Version 27.0 and summarized with descriptive statistics. Treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred or worsened at the time of or after administration of the bimatoprost implant. Analyses of CECD included mean CECD and mean percentage decrease in CECD from baseline.

For the analysis of GQL-15 results, total score was calculated as the sum of all 15 items. Subscale scores on each dimension were calculated as the sum of the items in the subscale. Total and subscale scores were both normalized to a range of 0–75.

Enrollment of approximately 228 patients was planned to provide at least 95% power to determine the proportion of patients without additional treatment in the primary eye at month 6 and later timepoints (months 9, 12, and 18) with a margin of error of 7%, based on an estimate from previous studies of 45% for the proportion of patients without additional treatment at month 6 and assuming both a trend for a decline in the proportion over time and a study discontinuation rate of 12%.

3 Results

3.1 Patient Disposition and Analysis Sets

A total of 217 patients (341 eyes) were enrolled, and 132 patients (60.8%) and 203 eyes (59.5%) completed the study (Fig. 1). Among the 125 eyes that discontinued from the study, the most common reason for study discontinuation (40 of 125 discontinued eyes, 32.0%) was loss to follow-up (Fig. 1). Only two eyes (0.6%) discontinued from the study because of an adverse event: one retinal edema attributed to the development of neovascular age-related macular degeneration and considered unrelated to treatment, and one increased IOP at 9 months. All 217 patients received a bimatoprost implant in the primary eye, and 210 patients had at least one post-administration assessment after the implant administration. The FAS of patients and eyes consisted of those 210 patients and the 210 primary eyes of those patients. As 128 patients received an implant in each eye, a total of 340 eyes were treated with the bimatoprost implant and included in the safety analyses.

3.2 Baseline Characteristics of Patients and Implant-Treated Eyes

Baseline characteristics of patients in the FAS are shown in Table 1. Most patients were White (68.6%) or Black or African American (18.6%), and the majority (57.6%) were female. The mean age was 73 years (range, 37–96). Table 2 lists baseline characteristics of the primary eyes in the FAS. Almost all eyes (97.6) were diagnosed with OAG, and the majority (69.5%) were pseudophakic. The severity of OAG was reported for 53 eyes: 13 mild, 21 moderate, and 19 severe. The iridocorneal angle was generally Shaffer grade 3 or 4 (Table 2). Most of the eyes were on topical IOP-lowering medication at baseline (45.2% on one medication, 17.1% on two medications, and 25.7% on more than two medications). The baseline mean IOP was 17.2 mm Hg on a mean of 1.8 IOP-lowering medications. The IOP-lowering medications most commonly used at baseline were PGAs, followed by beta-blockers, carbonic anhydrase inhibitors, alpha agonists, and rho kinase inhibitors.

Baseline characteristics in the safety analysis set of all implant-treated eyes were similar to those in the FAS (Table 2). Among all 340 primary and secondary eyes treated with the bimatoprost implant, 103 (30.3%) eyes had a history of glaucoma laser treatment (93 trabeculoplasty and 15 iridotomy), and 47 (13.8%) eyes had a history of incisional glaucoma surgery (30 iStent, 9 endocyclophotocoagulation, 9 goniotomy, 7 canaloplasty or viscocanaloplasty, 5 XEN gel stent, and 2 Hydrus).

3.3 Reasons for Use, Administration Procedure Setting, and Target IOP

The most common reasons for using the bimatoprost implant to lower IOP were categorized as intolerance to daily topical treatment (ocular surface disease) [38.5% (131/340) of eyes] and noncompliance with daily topical treatment [23.5% (80/340) of eyes] (Fig. 2). The implant administration procedure was performed in office for 69.7% (237/340) of eyes, in a free-standing ambulatory surgical center for 26.8% (91/340) of eyes, and in another setting for 3.5% (12/340) of eyes. The mean (SD) investigator-set target IOP

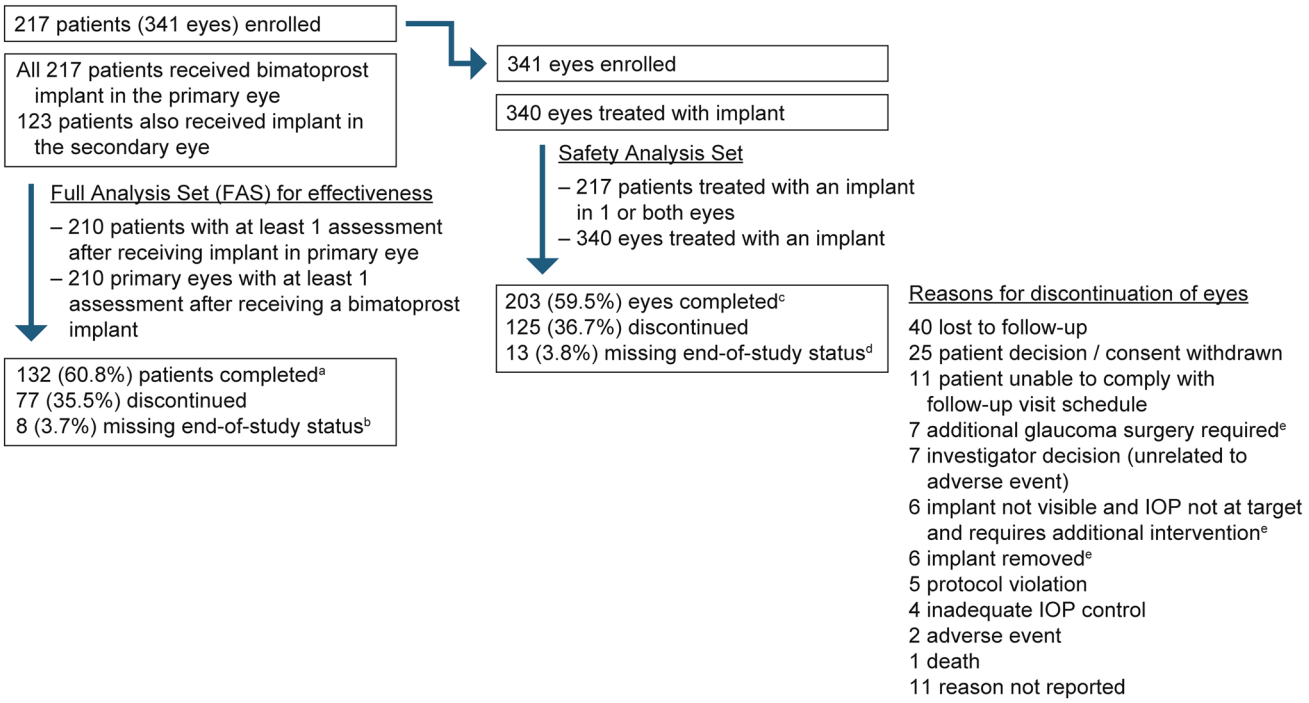


Fig. 1 Patient disposition. [a]A patient completed the study if the primary eye had 18 months of follow-up and a completed end-of-study case report form. [b]The end-of-study case report form for the primary eye was missing. [c]Eyes completed the study if they had 18 months of follow-up and a completed end-of-study case report form. [d]The end-of-study case report form for the eye was missing. [e]The original study protocol (before a protocol amendment) required that these eyes exit the study. *IOP* intraocular pressure

Table 1 Baseline characteristics of patients (full analysis set)

Parameter	Patients ($N = 210$)
Age, mean (SD), years	73.0 (9.75)
Range	37–96
Sex, *n* (%)	
Female	121 (57.6)
Male	89 (42.4)
Race, *n* (%)	
White	144 (68.6)
Black or African-American	39 (18.6)
Asian	9 (4.3)
Other	1 (0.5)
Not reported	17 (8.1)
Hispanic or Latino ethnicity, *n* (%)	16 (7.6)
Eye enrolled in study, *n* (%)	
Right eye only	39 (18.6)
Left eye only	43 (20.5)
Both eyes	128 (61.0)

SD standard deviation

for eyes treated with the implant was 15.2 (3.06) mm Hg (median, 15 mm Hg; range, 10–26 mm Hg).

3.4 Implant Location on Slit-Lamp Gonioscopy

The clock hour location of the implant in the iridocorneal angle was reported for 224 treated eyes. At the first follow-up visit with available data, the implant had settled in the inferior iridocorneal angle in most of those eyes, with 175 (78.1%) implants located at 5–7 o'clock, 14 (6.3%) implants located at 4–5 or 7–8 o'clock, and 35 (15.6%) implants located at other clock hours.

3.5 Effectiveness Outcomes

3.5.1 Proportion of Eyes Without Additional Treatment

In the primary analysis, the proportion of eyes that had received no additional treatment at month 6 (primary endpoint) was 88.6% (95% CI 86.6–90.6), and the proportion of eyes that had received no additional treatment at month 4 (key secondary endpoint) was 93.8% (95% CI 93.2–94.4). The proportion of eyes requiring no additional IOP-lowering treatment after implant administration remained high throughout 18 months of follow-up, with 83.7% (95% CI 80.2–87.3) of eyes having received no additional treatment at month 12, and 77.7% (95% CI 73.4–82.1) of eyes having received no additional treatment at month 18 (Fig. 3A). Results of the sensitivity

Table 2 Baseline characteristics of implant-treated eyes

Parameter	Primary (first treated) eye (FAS) ($N = 210$)	All treated eyes (safety set) ($N = 340$)
Diagnosis, *n* (%)[a]		
Open-angle glaucoma	205 (97.6)	332 (97.6)
Ocular hypertension	13 (6.2)	22 (6.5)
Angle grade (Shaffer)		
3	55 (26.2)	96 (28.2)
4	140 (66.7)	217 (63.8)
Other	1 (0.5)	2 (0.6)
Not reported	14 (6.7)	25 (7.4)
Lens status, *n* (%)		
Phakic	64 (30.5)	103 (30.3)
Pseudophakic	146 (69.5)	229 (67.4)
Not reported	0	8 (2.4)
Lens assessment of phakic eyes, *n* (% of phakic eyes)		
Clear	8 (12.5)	15 (14.6)
Opacity present, not visually significant	52 (81.3)	82 (79.6)
Visually significant opacity present	4 (6.3)	6 (5.8)
IOP, mean (SD), mm Hg	17.2 (4.74)	17.0 (4.57)
Range	8–33	8–33
Number of topical IOP-lowering medications at baseline		
0	25 (11.9)	37 (10.9)
1	95 (45.2)	164 (48.2)
2	36 (17.1)	58 (17.1)
> 2	54 (25.7)	81 (23.8)
Visual field MD, mean (SD), dB	− 3.0 (9.55)	−3.4 (9.52)
Range	− 31 to +28	−31 to +28
CECD,[b] mean (SD), cells/mm^2	NA	2169.1 (480.63)
Range	NA	577[c]–3649

CECD central corneal endothelial cell density, *FAS* full analysis set, *IOP* intraocular pressure, *MD* mean deviation, *NA* not analyzed, *SD* standard deviation

[a]Some eyes had > 1 diagnosis recorded during the baseline period

[b]Evaluated by reading center

[c]A few eyes in the FAS did not meet the inclusion criterion for CECD to be ≥ 2000 cells/mm^2

analysis using observed values were similar (Fig. 3B). Based on observed values, the proportion of eyes that had received no additional treatment was 93.8% (197/210) at month 4, 89.0% (162/182) at month 6, 84.6% (132/156) at month 12, and 79.0% (109/138) at month 18.

Within the FAS of 210 primary eyes that received a bimatoprost implant and had a post-administration assessment, 169 (80.5%) received no additional treatment during the study, and 41 (19.5%) received additional treatment. The probability of not requiring additional treatment at 18 months, estimated with Kaplan–Meier survival analysis, was approximately 80% (Fig. 4). Among the 41 eyes that received additional treatment, the median time to the first use of additional treatment was 17.6 months (range, 0.03–27.63).

3.5.2 IOP and Use of Topical IOP-Lowering Medications

Analysis of IOP after the bimatoprost implant administration in primary eyes showed reduced IOP through 18 months

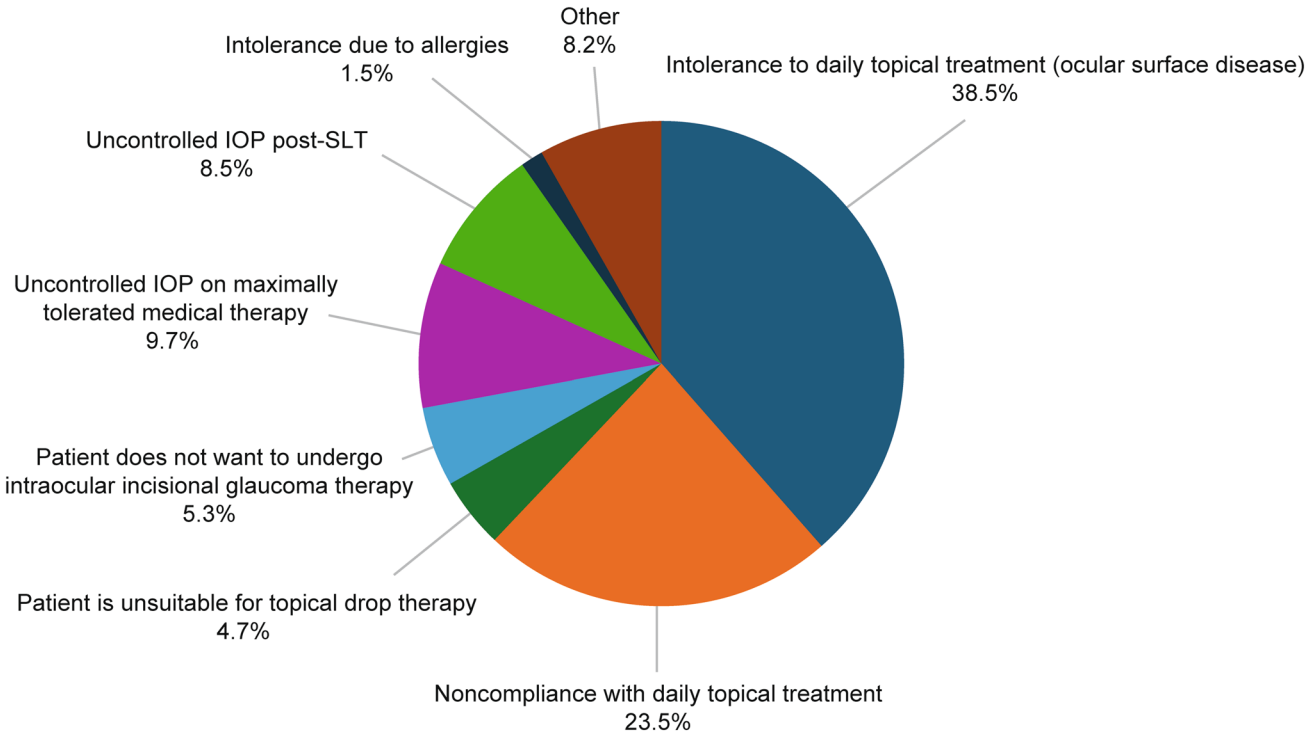


Fig. 2 Reasons for using the bimatoprost implant to lower intraocular pressure (IOP). The chart shows the percentage of eyes ($n = 340$) treated with the implant for each reason. *SLT* selective laser trabeculoplasty

of follow-up (Fig. 5). The mean number of topical IOP-lowering medications used also was decreased throughout the follow-up period, from 1.8 at baseline to 1.4 at month 4, 0.9 at months 6, 9, and 12, and 1.0 at month 18 (Fig. 5). The mean changes in IOP from baseline at follow-up visits ranged from − 1.0 to − 2.0 mm Hg, while the mean change from baseline in number of topical medications used was − 0.3 at month 4, − 0.9 at month 6, − 0.8 at months 9 and 12, and − 0.7 at month 18. The proportion of primary eyes that were drop free increased after the bimatoprost implant administration and remained increased through 18 months of follow-up (Fig. 6). The medication counts were conservative; for example, the number of medications used at month 4 counted all medications used at any time from the day of the implant to month 4. Nonetheless, the results suggest that in some eyes, topical medication use was stopped at weeks or months after the implant administration, after the effects of the implant on IOP were evaluated.

Topical PGAs were the medications most commonly used at baseline; the topical medication count at baseline included a PGA in 157 of the 210 primary eyes. After the implant administration, the topical PGA was discontinued in 146 primary eyes and continued in 11 primary eyes (two on a fixed combination containing PGA). Among the 146 primary eyes that stopped PGA use, 20 eyes restarted a PGA at a median time of 168 days after the implant administration.

The bell curve of the distribution of IOP values at baseline and months 6, 12, and 18 showed narrowing at follow-up visits; the mean, median, and maximum values were shifted to a lower IOP while the minimum values were generally unchanged (Fig. 7). These results suggest that eyes with higher IOP (≥ 17 mm Hg) at baseline were most likely to show reduced IOP after the bimatoprost implant administration.

3.6 Safety Outcomes

Ocular TEAEs were reported in 23.8% of implant-treated eyes (Table 3). The most commonly reported ocular TEAEs were increased IOP, dry eye, and OAG, reported in 6.8%, 5.0%, and 1.8% of eyes, respectively. The occurrence of all TEAEs including increased IOP was based on the clinical judgment of the investigator; the study protocol did not specify a particular magnitude of IOP increase that would

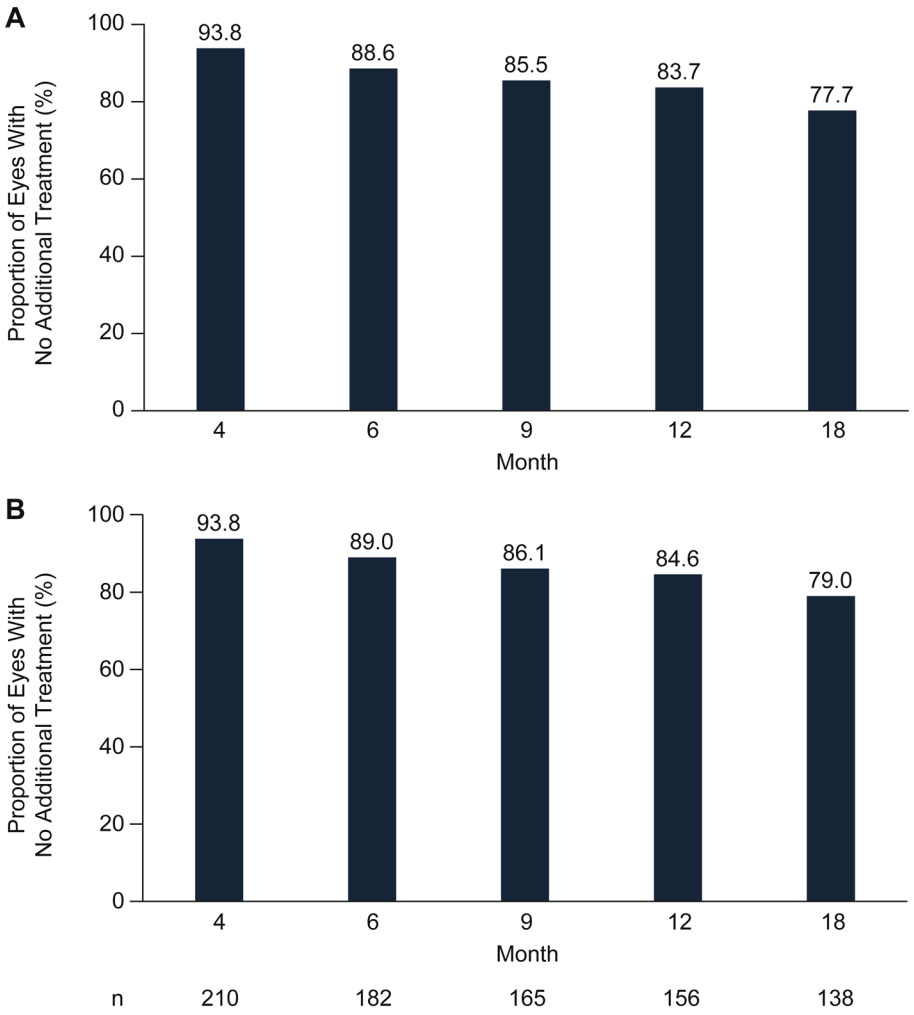


Fig. 3 Proportion of primary eyes (full analysis set) that received no additional (new) intraocular pressure–lowering treatment after the bimatoprost implant administration. **A** Proportion of eyes ($n = 210$) with no additional treatment at each visit estimated using logistic regression models with multiple imputation for eyes with missing data. **B** Proportion of eyes with no additional treatment at each visit based on the number of eyes with data available (observed data)

be considered a TEAE. Corneal ECL was reported in five eyes (1.5%) and conjunctival edema was reported in two eyes (0.6%). Iritis or iridocyclitis was reported in five eyes (1.5%). Conjunctival hyperemia was reported in one eye (0.3%). There were no reports of endophthalmitis or periorbital fat atrophy.

Treatment-emergent adverse events led to implant removal in five treated eyes (5/340, 1.5%), and these eyes subsequently were discontinued from the study. Four of the implant removals were in two patients. Implants were removed from both eyes of a patient with bilateral corneal ECL and iridocyclitis (ongoing from study entry). These TEAEs were reported as recovered with sequelae at study exit. Implants were also removed from both eyes of a patient with bilateral increased IOP and punctate keratitis in one eye. The patient had corneal dystrophy (a contraindication for implant use) so should not have received the implant. The TEAEs in both eyes were reported to be recovering at study exit. Finally, an implant was removed from an eye because of corneal edema and decreased visual acuity, which were reported to be recovering at study exit. In addition to the five implant removals because of TEAEs, one eye underwent an implant removal not associated with a TEAE; the implant in this eye was removed because the eye underwent intraocular surgery.

Mean CECD values from autocounts were higher than those from CRC readings (Fig. 8). Both methods of evaluation showed small changes in the mean CECD in implant-treated eyes during the 18-month follow-up, which were likely influenced by differences in the subset of eyes with data available at the various visits (Fig. 8). At month 18, the mean (SD) percentage change from baseline in CECD in implant-treated eyes was − 3.47 (9.047)% [$n = 131$] based on CRC evaluations and − 3.23 (14.966)% [$n = 143$] based on autocounts.

The BCVA and visual fields in treated eyes were generally stable over the course of the study. The mean BCVA was 0.2 logMAR (20/32 Snellen equivalent) at each visit, and the mean (SD) change in BCVA from baseline at month 18 was 0.0 (0.17) logMAR ($n = 202$). The mean (SD) visual field mean deviation change from baseline at month 18 was 0.1 (3.14) dB ($n = 159$).

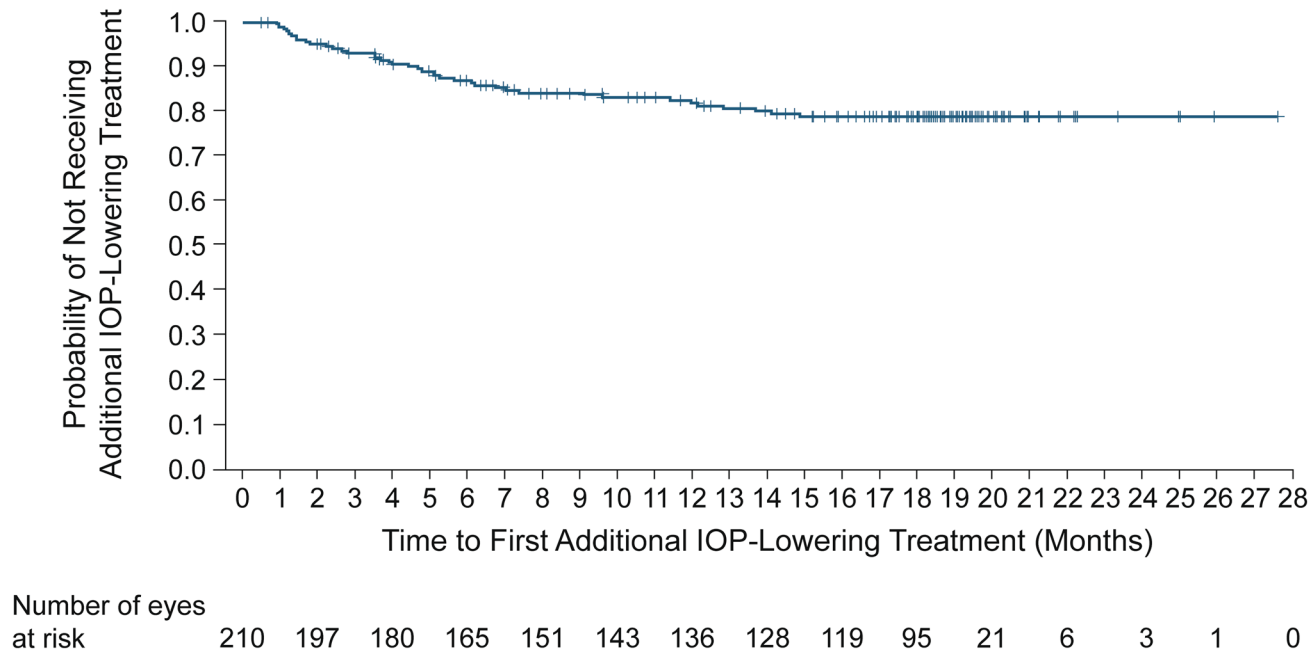


Fig. 4 Kaplan–Meier survival analysis of time to initial use of additional treatment after the bimatoprost implant administration in primary eyes (full analysis set). *IOP* intraocular pressure

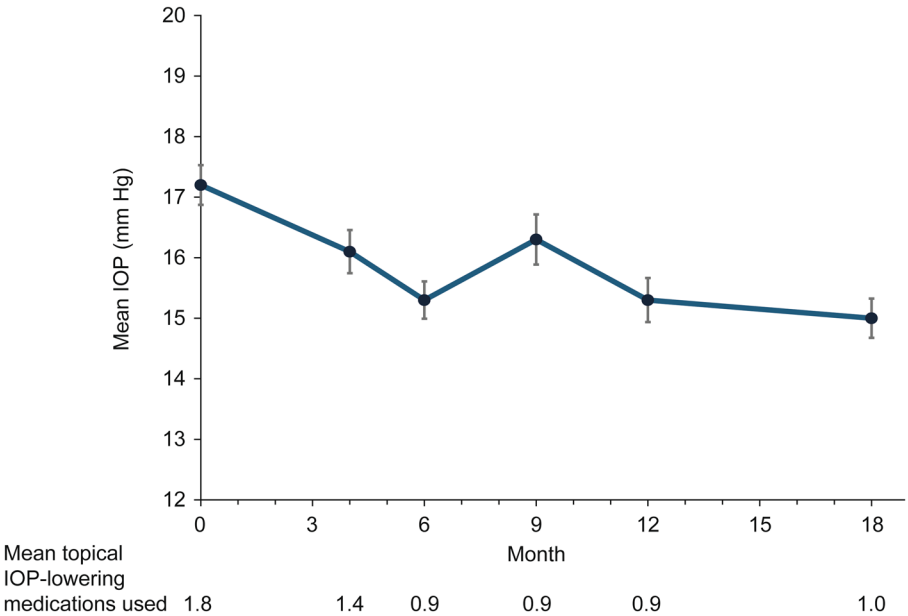


Fig. 5 Mean intraocular pressure (IOP) and mean number of topical IOP-lowering medications at baseline and after bimatoprost implant administration in primary eyes (full analysis set). The number of eyes with data available for analysis at baseline and months 4, 6, 9, 12, and 18, respectively, was 209, 201, 141, 123, 129, and 135 for IOP and 210, 210, 182, 165, 156, and 138 for the number of medications used. Error bars show the standard error of the mean

3.7 Patient-Reported Outcomes

Data on the burdensomeness of the bimatoprost implant administration procedure were available for 127 patients after the initial (primary eye) administration and 47 patients after the administration in the secondary eye. The majority of patients reported that the procedures in the primary and secondary eye were much less burdensome than expected (Fig. 9).

Patients who were enrolled after the study protocol amendment were administered the GQL-15 questionnaire at baseline and the final visit for each implant-treated eye. The questionnaire was completed at the baseline visits for 25 eyes (15 primary and 10 secondary), as well as at the final visits for 25 eyes (16 primary and 9 secondary). There were

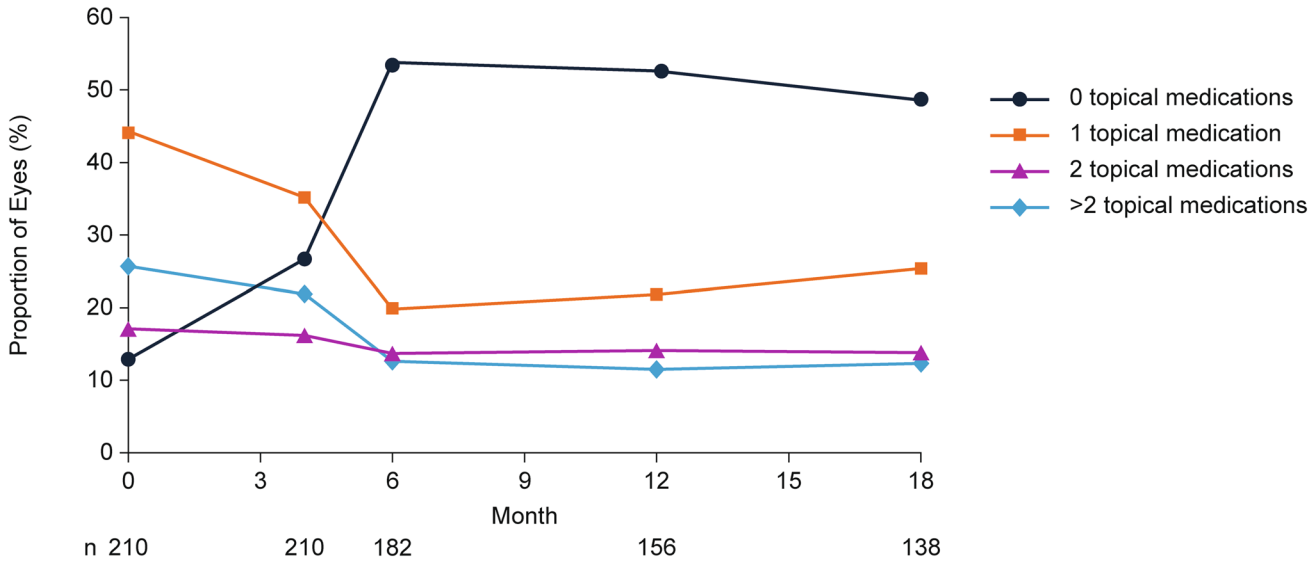
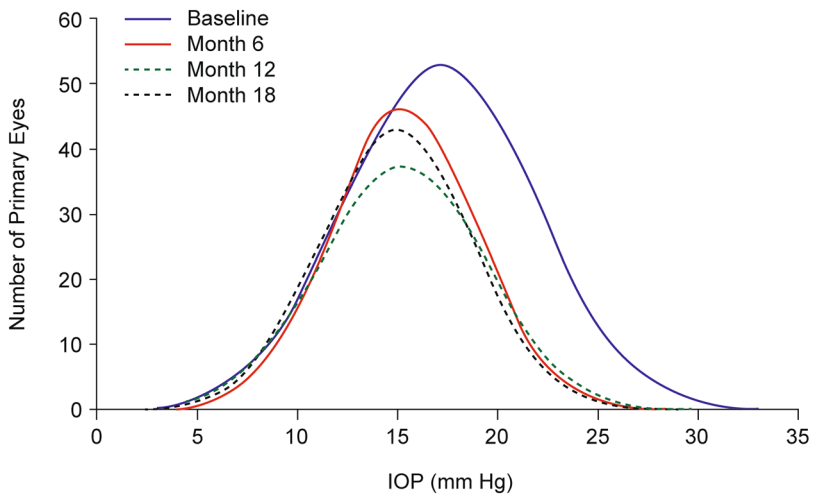


Fig. 6 Proportion of primary eyes (full analysis set) on 0, 1, 2, or > 2 topical intraocular pressure–lowering medications based on the number of eyes with data available at each visit



Analysis window	Mean (SD) number of topical IOP-lowering medications used
Baseline (n=210)	1.8 (1.41)
Month 6 (n=182)	0.9 (1.19)
Month 12 (n=156)	0.9 (1.21)
Month 18 (n=138)	1.0 (1.21)

Fig. 7 Distribution of intraocular pressure (IOP) values in primary eyes (full analysis set) at baseline and months 6, 12, and 18. Each bell curve was generated with the kernel density estimation method assuming a normal distribution. The mean target IOP in the safety analysis set was 15.2 mm Hg. *SD* standard deviation

no notable differences in total GQL-15 scores or scores on the GQL-15 subscales (central and near vision, peripheral vision, dark adaptation and glare, and outdoor mobility) between the baseline and final visits (Table 4).

A total of 25 patients consented to be interviewed and participated in qualitative interviews about their treatment experience at 4–6 months after the implant administration. Among the interview participants, 14 (56%) were on monotherapy for glaucoma at the time of screening, and 11 (44%) were on combination therapy. Almost all (96%, 24 of 25) reported having used eye drops to lower their IOP, and the majority of participants with eye drop experience (54.2%, 13 of 24) reported that the eye drops had side effects such as eye redness, burning sensation, and dry eye. Approximately half of the participants (48%, 12 of 25) reported having previous laser therapy to lower IOP. Regarding their expectations of the bimatoprost implant, most patients with evaluable data (84.6%, 11 of 13) had expected to reach their target IOP after

Table 3 Ocular TEAEs (safety analysis set)

TEAE, *n* (%)	All eyes (*N* = 340)	Primary eye (*N* = 217)	Secondary eye (*N* = 123)
Any ocular TEAE	81 (23.8)	59 (27.2)	22 (17.9)
IOP increased	23 (6.8)	20 (9.2)	3 (2.4)
Dry eye	17 (5.0)	10 (4.6)	7 (5.7)
Open-angle glaucoma	6 (1.8)	6 (2.8)	0
Corneal endothelial cell loss	5 (1.5)	3 (1.4)	2 (1.6)
Visual acuity reduced	5 (1.5)	5 (2.3)	0
Cataract nuclear	4 (1.2)	2 (0.9)	2 (1.6)
Conjunctivitis allergic	4 (1.2)	3 (1.4)	1 (0.8)
Eye irritation	4 (1.2)	2 (0.9)	2 (1.6)
Macular edema	4 (1.2)	2 (0.9)	2 (1.6)

All TEAEs reported in ≥ 1% of the implant-treated eyes are listed

IOP intraocular pressure, *TEAE* treatment-emergent adverse event

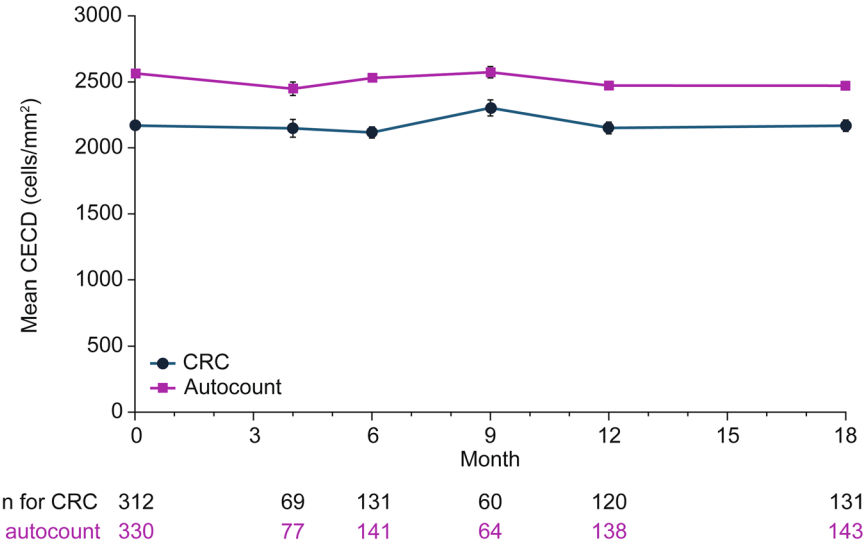


Fig. 8 Mean central corneal endothelial cell density (CECD) on specular microscopy (safety analysis set). Cell density was evaluated using autocounts and central reading center (CRC) evaluations. Error bars show the standard error of the mean

receiving the bimatoprost implant, and almost all patients with evaluable data (94.4%, 17 of 18) had expected to reduce or stop their use of eye drops after receiving the bimatoprost implant.

Most interview participants (84%, 21 of 25) reported overall satisfaction with the results of their implant treatment; one participant (4%) was dissatisfied because of an increase in IOP after the procedure. Benefits of the procedure reported by participants included a decrease in elevated IOP (reported by 48%, 12 of 25), improvement in mental health (commonly described as decreased anxiety and fear related to potential future blindness, and reported by 46.7%, 7 of 15), and a decrease in the use of eye drops after receiving the implant (reported by 25%, 6 of 24). When asked about their preference for treatment with the bimatoprost implant, eye drops, or both the implant and drops, the majority of participants (76%, 19 of 25) reported a preference for treatment with the bimatoprost implant alone.

4 Discussion

This study evaluated the use and outcomes of bimatoprost implant treatment in a real-world population of patients who received the implant per standard medical care. The results showed that bimatoprost implant was used as monotherapy or as adjunctive therapy with ongoing topical medications. After the implant administration in the primary eye, most patients (estimated 77.7%) had controlled IOP for up to 18 months without any new topical medication or procedure. On average, both IOP and the use of topical IOP-lowering medications were reduced from

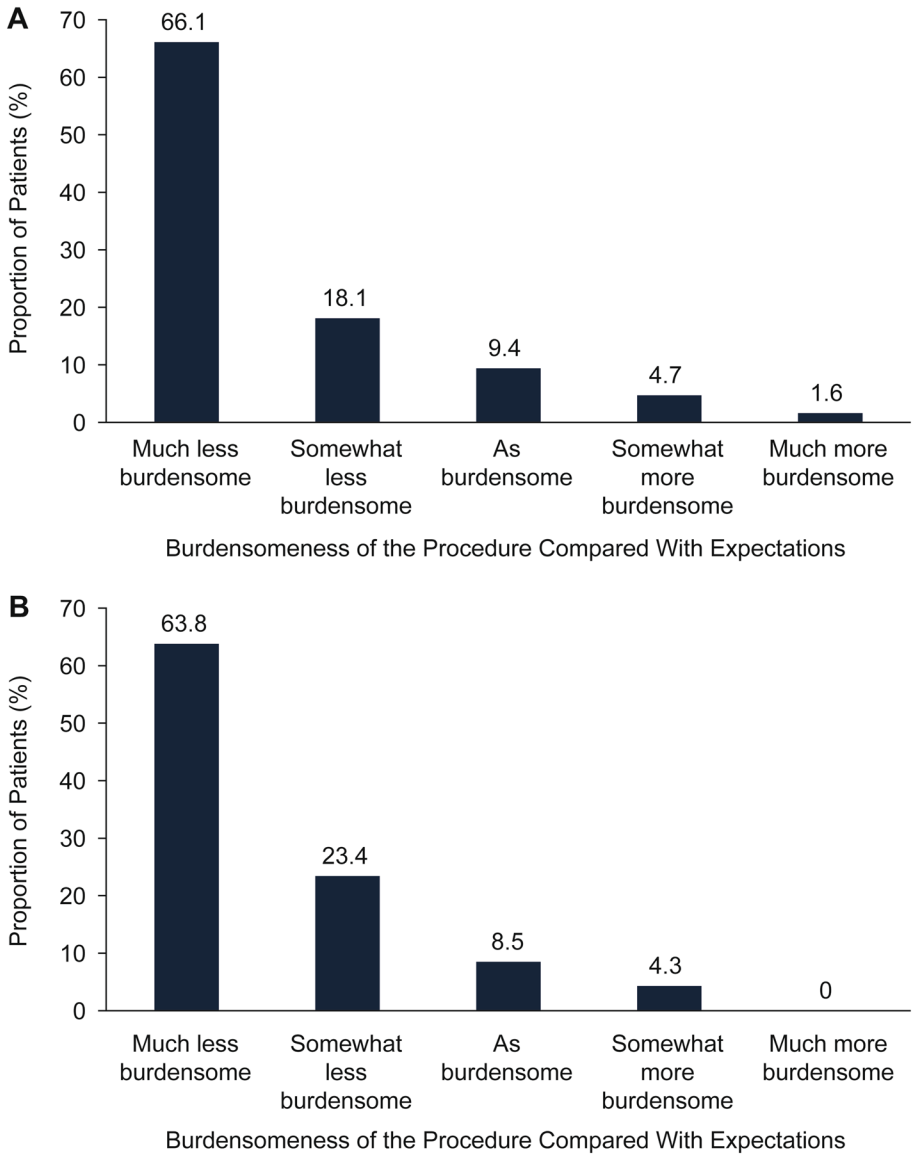


Fig. 9 Proportion of patients reporting defined levels of burdensomeness of the implant administration procedure, relative to their expectations, at the first follow-up visit post-administration. **A** Burdensomeness of the procedure reported by 127 patients after the primary eye administration. **B** Burdensomeness of the procedure reported by 47 patients after the secondary eye administration

baseline throughout the 18-month follow-up period. At 12 months, the average reduction in IOP from the medicated baseline was approximately 2 mm Hg (mean: 1.6, median: 2 mm Hg), and on average, patients had reduced their topical medication use by approximately one medication (mean: 0.8, median: 1 medication). The bimatoprost implant was well tolerated and had an acceptable safety profile. Patients generally reported that the implant administration procedure was less burdensome than expected and they were satisfied overall with their treatment outcomes.

The bimatoprost implant demonstrated effectiveness in a diverse patient population in this study. Although almost all eyes treated with the bimatoprost implant were diagnosed with OAG, the severity of disease varied from mild to severe. Most eyes were on eye drop therapy for their IOP, and one quarter of the eyes were being treated with three or more topical medications, suggesting that many of the eyes in this real-world study were more difficult to treat than those in the registration trials of the bimatoprost

Table 4 Patient scores on the GQL-15 questionnaire before and approximately 18 months after bimatoprost implant administration

GQL-15 questionnaire	Baseline ($n = 25$)	Final visit ($n = 25$)
Total score		
Mean (SD)	27.0 (12.21)	29.1 (12.64)
Median	22.0	25.7
Range	16–57	15–54
Subscale: central and near vision		
Mean (SD)	25.8 (14.54)	26.4 (17.87)
Median	22.5	15.0
Range	15–68	15–68
Subscale: peripheral vision		
Mean (SD)	25.6 (13.80)	27.2 (13.87)
Median	17.5	25.0
Range	15–60	15–65
Subscale: dark adaptation and glare		
Mean (SD)	30.0 (11.73)	32.6 (13.02)
Median	27.5	32.5
Range	18–53	15–55
Subscale: outdoor mobility		
Mean (SD)	18.6 (9.95)	23.4 (17.90)
Median	15.0	15.0
Range	15–45	15–75

GQL-15 Glaucoma Quality of Life 15-item, *SD* standard deviation

implant, which enrolled patients whose IOP could be controlled with a single topical medication [27, 29].

A major benefit of sustained-release drug delivery in glaucoma is the reduction or elimination of the need for daily eye drops to control IOP [26, 38], and in this study, the decision to use the bimatoprost implant was usually made because the patient was intolerant of or nonadherent to topical IOP-lowering medications. On average, patients were able to decrease their use of topical medications after receiving the implant. The progressive decrease in the mean number of medications used from month 4 to month 6 suggests that in some cases investigators discontinued topical medications shortly before or when patients received the implant, but in other cases, tapered the use of topical medications after checking the effect of the implant on IOP.

The average target pressure for the implant-treated eyes (15 mm Hg) was less than the medicated IOP of the eyes at baseline (17 mm Hg), suggesting that the bimatoprost implant was also used to provide additional IOP lowering. The observed distribution of IOP values in implant-treated eyes at baseline and months 6, 12, and 18 suggests that eyes with a higher IOP at baseline were likely to have reduced IOP after receiving the implant, and eyes with a lower IOP at baseline were likely to have stable IOP. These results are consistent with findings of a large retrospective single-site study recently reported by Sarkisian and Mitchell [35]. In that study, eyes with a baseline IOP ≥ 21 mm Hg ("uncontrolled IOP") demonstrated a significant reduction in IOP at 6 months after receiving the bimatoprost implant, whereas eyes with a baseline IOP < 21 mm Hg ("controlled IOP") had a reduction in medication use but no change in IOP at 6 months after the bimatoprost implant [35]. Together these results suggest that in clinical practice, the bimatoprost implant reduces the eye drop burden in eyes with controlled IOP and reduces IOP as well as the eye drop burden in eyes with elevated IOP.

The decreases in IOP and use of topical medications seen after bimatoprost implant treatment in this study are consistent with the results of previously reported retrospective studies of real-world bimatoprost implant use [33–36]. In a study in 38 patients with OAG or OHT, 31 of 46 eyes (67.4%) did not restart topical IOP-lowering medication or require an IOP-lowering procedure over a mean follow-up period of 274 days after receiving a bimatoprost implant [33]. In a large case series of 197 eyes (105 patients) with OAG or OHT, topical medication use was reduced and the mean IOP was lowered for up to 1 year after the eyes received bimatoprost implant treatment [34]. Sarkisian and Mitchell [35] reported a similar large case series of 197 eyes (105 patients) with OAG or OHT. After bimatoprost implant administration, the mean IOP in the implant-treated eyes was reduced from baseline for up to 1 year, and the mean number of topical IOP-lowering medications used was reduced from 1.4 at baseline to 0.2 at 11–13 months. Finally, in a case series of 129 eyes (81 patients), most diagnosed with primary OAG [36], topical IOP-lowering medication use was reduced and eyes had a 40.5% probability of not requiring any added IOP-lowering treatment through 12 months after receiving the bimatoprost implant [36].

The most common adverse event in this study was increased IOP, which is expected to occur when the implant effect wears off. By contrast, in the ARTEMIS registration trials of the bimatoprost implant, the most common adverse event was conjunctival hyperemia, which usually occurred within 2 days of the implant administration and was believed to be caused by the use of povidone iodine in the sterile preparation for the procedure [27, 29]. In this real-world study, there was only one report of conjunctival hyperemia, and the investigator deemed it unrelated to both the drug and the administration procedure. The lack of conjunctival hyperemia event reports may reflect the absence of a follow-up visit with biomicroscopy assessments within 1 or 2 days of the implant administration in real-life clinical practice. Any events potentially related to the administration procedure that occurred (such as conjunctival hyperemia, eye irritation, and foreign body sensation) were rarely reported by patients. Corneal ECL was reported in five (1.5%) implant-treated

eyes, a much lower incidence than in the ARTEMIS trials, where eyes received three administrations of the implant on a fixed 16-week dosing schedule.

Specular microscopy showed minimal changes in mean CECD over the 18-month follow-up period. Autocounts of CECD were consistently higher than the central reader evaluations of CECD, but with each method of assessment, the percentage loss in mean CECD was 3.2–3.5% over 18 months. The rate of ECL following the implant administration was somewhat higher than the average 0.6%/year associated with aging [39] but similar to that following a single 360° selective laser trabeculoplasty procedure [40]. When necessary, the bimatoprost implant is removed with a standard aseptic anterior chamber washout procedure [27]. In this study, implant removal was required in five (1.5%) treated eyes because of TEAEs, which were related to corneal edema or ECL in three of the five eyes.

The limitations of this study include the low study completion rate, which included a loss to follow-up of 40 (11.8%) implant-treated eyes. Lack of adherence to ophthalmic follow-up visits is a well-recognized problem in glaucoma management [41, 42], and other prospective real-world studies in patients with glaucoma have reported similar rates of loss to follow-up [43]. Because follow-up visits were scheduled at the discretion of the investigators according to their clinical judgment and the local standard of care, some patients who remained in the study had missing data at timepoints of interest because they were not seen within the corresponding visit windows. Additionally, the final study protocol excluded eyes with prior intraocular procedures that could have confounding effects on CECD, but under the initial study protocol, some eyes with stents were enrolled, and those eyes were treated with the bimatoprost implant and included in the analysis.

Previous retrospective studies of the use of the bimatoprost implant in clinical practice have shown reductions in IOP and the use of topical medications for up to 1 year after implant administration [33–36]. In this prospective study, the period of follow-up was extended, and beneficial effects of the implant on IOP and medication use continued to be seen through 18 months. Other strengths of the study were the required use of specular microscopy, which is not standard care, to provide safety information regarding corneal health, and the use of interviews to elicit patients' perspectives. Patients voiced their expectations of the implant treatment and the acceptability of the procedure. Most of the patients were satisfied with the outcomes of their implant treatment and preferred the implant treatment over eye drops.

5 Conclusions

The objective of this study was to prospectively collect effectiveness and safety data after bimatoprost implant administration in patients who received the implant in real-world clinical practice. The collected data showed effectiveness of the bimatoprost implant in a diverse patient population. Both mean IOP and the mean number of topical medications used were reduced after the implant administration, and beneficial effects of the implant on IOP and medication burden were sustained throughout the 18-month study. The safety profile of the implant was acceptable.

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Declarations

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Conflicts of Interest/Competing Interests Eric Mann and Gagan Sawhney are speakers for AbbVie. Jeffrey A. Kammer has no disclosures. Jella An has previously served as a consultant for AbbVie. Erica C. Werts, Vanessa Vera, Marcos Rivas, Hongxin Lai, Sadhana Sonparote, and E. Randy Craven are employees of AbbVie and may hold AbbVie stock.

Ethics Approval Institutional review board or independent ethics committee approval was obtained at each site before the study began, and the study was performed in compliance with Good Clinical Practice, the principles of the Declaration of Helsinki, and applicable laws and regulations (ClinicalTrials.gov registration number NCT04647214).

Consent to Participate All patients in this study provided written informed consent before undergoing any study-related procedure.

Consent for Publication Not applicable.

Availability of Data and Material AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), provided the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous independent scientific research, and will be provided following review and approval of a research proposal, statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

Code Availability Not applicable.

Authors' Contributions Study design: ECW, VV, MR, ERC; data collection: EM, JAK, GS, JA; statistical analysis: HL; data interpretation: EM, JAK, GS, JA, ECW, VV, MR, HL, SS, ERC; drafting, revisions, and approval of the manuscript: EM, JAK, GS, JA, ECW, VV, MR, HL, SS, ERC.

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