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ORIGINAL RESEARCH ARTICLE

Safety and Longevity of Intraocular Pressure Control After Bimatoprost Implant Administration: Interim Analysis of a Phase 3b Clinical Trial (TRITON)

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Abstract

Background Bimatoprost implant 10 µg is an intracameral, biodegradable implant that slowly releases bimatoprost to lower intraocular pressure (IOP). This study was designed to evaluate safety and the duration of the IOP-lowering effect after single and as-needed repeat administration of the bimatoprost implant in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT).

Patients and Methods This study is an interim analysis of an ongoing, prospective, open-label, multicenter study in patients with OAG or OHT who are inadequately managed with topical IOP-lowering medication for reasons other than efficacy. IOP-lowering rescue treatment is allowed if implant retreatment criteria are not met. The primary endpoint is time to retreatment/rescue after the initial implant administration analyzed with the Kaplan–Meier method. Key safety measures include treatment-emergent adverse events (TEAEs) and reading-center evaluation of central corneal endothelial cell density (CECD). Analysis of data collected through 15 September 2023 focused on outcomes after a single or two implants.

Results In total, 441 patients received the 10-µg bimatoprost implant in the study eye on day 1 (cycle 1), 179 patients received a second administration (cycle 2), and 378 patients had at least 12 months of follow-up data available. The median time (95% confidence interval) from the first administration to a second administration or rescue was 392 (369, 485) days; the probability of not requiring retreatment or rescue by day 360 was 57.5%. A second implant administration similarly provided a long duration of IOP control. The baseline mean (standard error, SE) IOP was 25.6 (0.14) mmHg; the mean (SE) change from baseline IOP in unrescued eyes after a single administration was − 7.5 (0.21) mmHg at week 24 and − 6.4 (0.28) mmHg at month 12. Conjunctival hyperemia, typically associated with the administration procedure, was the most common ocular TEAE (cycle 1, 14.3%; cycle 2, 12.8%). Mean (SE) percentage change in CECD from baseline at 12 months after administration was − 4.3 (0.81)% in cycle 1 and − 8.5 (2.22)% in cycle 2. The cycle 1 implant was no longer visible or ≤ 25% of initial size in 66.3% and 94.3% of study eyes at months 12 and 24, respectively.

Conclusions In this interim analysis based on available data, the IOP-lowering effect of the initial administration of the 10-µg bimatoprost implant was well maintained for > 1 year in most patients. Results after a second administration were comparable. The safety profile of initial and repeat administration was acceptable.

Trial Registry ClinicalTrials.gov identifier NCT03850782; registered 20 February 2019.

1 Introduction

Open-angle glaucoma (OAG), a chronic disease that causes progressive vision loss, is highly prevalent and a leading cause of irreversible blindness [1]. A study using data available in 2014 projected that the global prevalence of primary OAG in individuals aged 40–80 years would be 53 million in 2020, increasing to 80 million in 2040 [2]. All approved treatments of OAG are aimed at lowering intraocular pressure (IOP). Reducing IOP has been demonstrated to slow the progression of glaucomatous visual field loss [3, 4] and

The TRITON Study Group Principal Investigators are listed in acknowledgements.

Extended author information available on the last page of the article

Key Points

Most eyes that were treated with a single bimatoprost implant had controlled intraocular pressure (IOP) without the use of eyedrops for longer than 1 year.

When the effects of the implant wore off and additional IOP lowering was needed, treatment with a second implant similarly resulted in a long duration of IOP control.

The safety profile of the initial administration and a single repeat administration was acceptable.

decrease the risk that individuals with ocular hypertension (OHT) develop glaucoma [5].

Topical ocular hypotensive medication is the standard first-line treatment for OAG and OHT [6, 7]. However, patient adherence to IOP-lowering eyedrops is frequently poor [8, 9], with an estimated 30–80% of patients not using their medication as prescribed [10–12]. Forgetfulness, inconvenience, physical inability to instill the drops, side effects, cost, and lack of understanding of the importance of medication use are among the numerous reasons for patient nonadherence to IOP-lowering eyedrops [13–17]. Importantly, poorer adherence to topical IOP-lowering medication is associated with worse visual field progression [18, 19].

Biodegradable, sustained-release bimatoprost implant 10 µg (Durysta; AbbVie, North Chicago, IL, USA) was developed to address the problem of nonadherence to topical IOP-lowering medications in glaucoma [20]. The cylindrical implant (diameter ~200 µm, length ~1.1 mm) consists of 10 µg bimatoprost in a matrix of poly-lactic acid and polylactic-co-glycolic polymers [21]. The implant is administered intracamerally with a single-use, 28-gauge applicator and was designed to provide continuous release of bimatoprost for 3–4 months [21] as the polymer matrix is metabolized and hydrolyzed to carbon dioxide and water [22]. Multiple phase 3 clinical trials [21, 23, 24] have demonstrated effectiveness of the bimatoprost implant in reducing IOP without the use of eyedrops in individuals with OAG and OHT. The duration of IOP-lowering effect has been shown to be longer than the expected duration of ocular bioavailability of bimatoprost after implant administration [21, 23–25]. Bimatoprost implant 10 µg currently is approved in the USA for single use per eye to lower IOP in OAG and OHT [23].

During the development of the bimatoprost implant, a phase 3b clinical study (TRITON) was initiated to evaluate the duration of IOP-lowering effect and safety of up to three pro re nata (PRN) administrations of the bimatoprost implant in the study eye of patients with OAG or OHT not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy (e.g., because of intolerance or nonadherence). Under the original protocol, patients were randomized to receive a 10- or 15-µg dose strength of the bimatoprost implant in a masked fashion. However, a protocol amendment discontinued the use of the 15-µg implant, and the study became an open-label, single-arm study with all newly enrolled patients receiving the 10-µg dose strength of the bimatoprost implant.

The TRITON study is ongoing with anticipated completion in August 2025. A planned interim analysis of the study results was conducted using all available data collected through 15 September 2023. This interim report evaluates the duration of effect after the initial and a second as-needed administration of bimatoprost implant 10 µg in the study eye, as well as safety outcomes in all patients treated with the 10-µg bimatoprost implant.

2 Patients and Methods

2.1 Study Design

This ongoing, open-label, prospective, phase 3b, multicenter study is evaluating the duration of the IOP-lowering effect and safety of single and as-needed repeat administration of bimatoprost implant 10 µg in patients with OAG or OHT not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy. The study duration is a minimum of 30 months and up to 48 months. The first patient study visit was on 28 February 2019. Under the original study protocol, patients were randomly assigned to treatment with either a 10- or 15-µg dose strength of the bimatoprost implant. However, the 10-µg bimatoprost implant was approved by the US Food and Drug Administration in March 2020, and the 15-µg bimatoprost implant was discontinued from development. Thus, a protocol amendment in March 2020 discontinued use of the 15-µg bimatoprost implant, and those patients who had been treated with the 15-µg implant dose strength of implant received no additional study treatment. With the implementation of the protocol amendment, the study became an open-label, single-arm study evaluating the 10-µg bimatoprost implant (Fig. 1). Potential interim database locks were included in the study protocol to support regulatory submissions. Data collected through 15 September 2023 for patients who received the 10-µg bimatoprost implant are analyzed in this interim report.

The study was conducted in accordance with the International Conference for Harmonization 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 NCT03850782.

2.2 Study Population

A complete listing of all patient eligibility criteria is provided in Online Resource 1. The study enrolled adults with OAG or OHT requiring IOP-lowering treatment in the study eye. The study eye was required to have an open inferior iridocorneal angle (inferior angle Shaffer grade of ≥ 3 on gonioscopy with peripheral anterior chamber depth of ≥ 0.5 corneal thickness by Van Herick examination); central corneal endothelial cell density (CECD) at screening of ≥ 2000 cells/mm^2 by automated analysis; and IOP ≥ 22 and ≤ 34 mmHg at the baseline visit (9:00 ± 1 h) after washout in the study eye. Other key inclusion criteria included the investigator's determination that the patient's IOP was not adequately managed with topical medication for reasons other than medication efficacy and the investigator's determination that IOP in the study eye could be treated adequately with topical prostaglandin analog/prostamide (PGA) monotherapy if the medication was taken as directed. Key exclusion criteria were any previous treatment with a bimatoprost implant in the study eye; history of laser trabeculoplasty or glaucoma surgery in the study eye; history or evidence of clinically relevant, substantial ocular trauma in the study eye; history or evidence of complicated cataract surgery or intraoperative complications in the study eye; and history of phakic intraocular lens insertion for refractive error correction in the study eye. Patients with functionally significant visual field loss in either eye were excluded.

If both eyes met the study eye entry criteria, the eye with the higher IOP at baseline (or the right eye, if both eyes had the same IOP) was selected as the study eye.

2.3 Screening, Enrollment, and Visit Schedule

Patients were screened over a period of up to 10 days. After completing all screening procedures, patients treated with IOP-lowering medication(s) in either eye discontinued the medication(s) and began a washout period of up to 56 days before the baseline visit(s). The minimum washout period was 4 days for parasympathomimetics and carbonic anhydrase inhibitors, 14 days for sympathomimetics and alpha-agonists, and 28 days for beta-blockers, rho kinase inhibitors, and PGAs.

Eligible patients were enrolled in the study after baseline assessments, which were conducted over a period of up to 3 days. Patients who completed all visits through month 48/exit had a minimum of 31 visits, including screening and baseline visits, visits during the PRN treatment period (minimum of 18 and up to 36 months), and visits during an extended follow-up period of at least 12 months after the last administration (Fig. 1).

2.4 Study Treatment and Rescue

On day 1, patients were administered bimatoprost implant 10 µg in the study eye, and the fellow eye began standard-of-care (SOC) topical IOP-lowering therapy that, in the investigator's opinion, would have no crossover effect in the study eye. Up to two retreatments with the implant were allowed in the study eye, each at least 16 weeks after the last implant

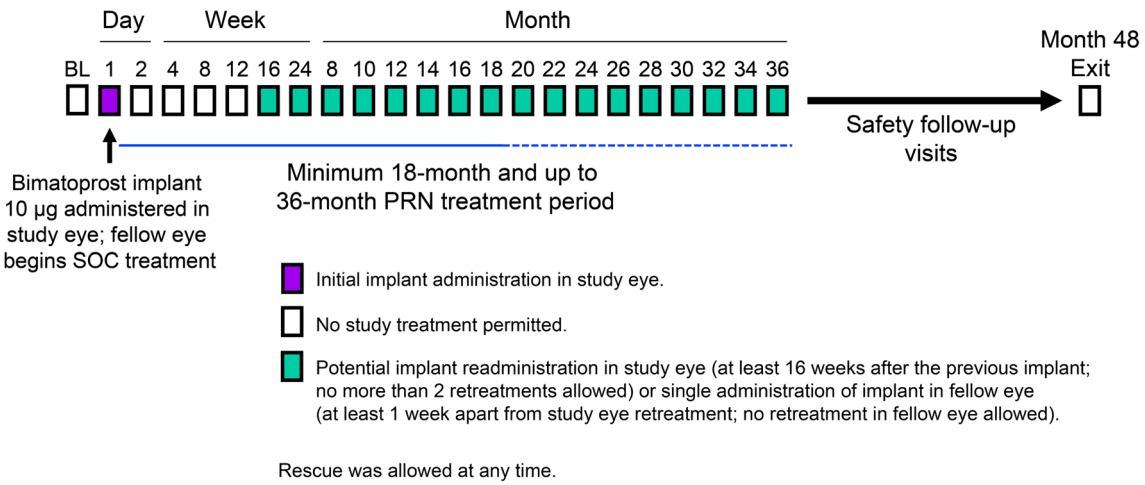

Fig. 1 Study schematic. After bimatoprost implant readministration in the study eye, patients were seen at visits 1 day and 4, 8, 12, and 16 weeks after the readministration, then returned to the original study visit schedule. The recommended time for fellow eye administration in eyes that met eligibility criteria was 1–3 weeks after implant readministration in the study eye; a safety visit was scheduled for the day after the fellow eye administration visit. *BL* baseline, *PRN* pro re nata, *SOC* standard-of-care

administration, during the PRN treatment period (minimum of 18 and up to 36 months) only. For each implant administration, the eye was prepared for intraocular injection using standard aseptic procedure, and the implant was administered intracamerally by the investigator using a single-use, prefilled applicator system [21].

Patients received up to three as-needed administrations of bimatoprost implant 10 µg in the study eye. The decision to readminister implant in the study eye included consideration of IOP or disease worsening, size of the residual implant, time since the last implant administration, the number of implant administrations within 12 months (a maximum of two administrations were allowed in any 12-month period), and safety. Study eyes were eligible for retreatment if all of the following criteria were met: (1) the investigator determined that there was a clinically meaningful increase in IOP that was confirmed at a subsequent visit not on the same day, and/or there were clinical signs or symptoms of disease worsening (e.g., disc hemorrhage or worsened visual field); (2) each previously administered implant was < 25% of its original size; (3) at least 16 weeks had passed since the previous administration; (4) the eye had received no more than one administration during the previous 12 months; (5) the eye had not received rescue treatment other than topical IOP-lowering medication used temporarily (until the eye met all retreatment criteria) and discontinued at least 1 day before the retreatment; and (6) in the investigator's opinion, it was safe for the eye to receive an additional administration of the implant. Significant corneal findings (such as corneal edema) related to the presence of the implant, CECD < 2000 cells/mm^2 by automated analysis of specular microscopy (confirmed at two consecutive visits on separate days), a persistent and progressive ≥ 15% CECD decrease from baseline (confirmed at two consecutive visits on separate days), the presence of remnant implant that on the basis of its size or position would prevent safe administration of another implant, and clinically significant intraocular inflammatory findings at any visit (other than mild intraocular inflammation related to the administration procedure that resolved rapidly) precluded readministration of the implant. The requirement for at least 16 weeks between implant administrations was based on previous clinical studies that used a 16-week fixed dosing interval [21, 23] and a preclinical study in dogs, in which intraocular drug levels were measurable through 80 days and were beneath the limit of quantitation at 4.2 months after bilateral administration of a 15-µg bimatoprost implant [21].

A single implant administration was permitted in eligible fellow eyes during the period from week 16 through completion of the PRN treatment period. The fellow eye administration was at least 1 week apart from a study eye administration, and the recommended timing of fellow eye administration was 1–3 weeks after implant readministration in the study eye. The criteria for fellow eyes to be eligible for implant administration (Online Resource 2) were generally similar to the study eye criteria for patient entry, but there was no requirement regarding the baseline IOP, and there were added requirements of no significant corneal findings potentially resulting from the implant in the study eye and no progressive, confirmed ≥ 15% CECD loss in the study eye. For fellow eyes that received implant administration, SOC treatment was stopped at least 1 day before the administration.

For patients who both did not meet IOP-lowering expectations and did not meet retreatment criteria, rescue treatment (IOP-lowering medication or procedure) could be initiated after confirmation of inadequate IOP control at a subsequent visit.

2.5 Assessments and Outcome Measures

Efficacy assessments included IOP and the investigator-determined need for retreatment or rescue. IOP was measured at 9:00 a.m. (± 1 h) at all visits except the administration day visits using Goldmann applanation and a two-person reading method [26]. For each eye, the mean of two measurements, or the median of three measurements (if the first two measurements differed by > 1 mmHg), was used for analysis.

Safety assessments included adverse events at each visit, biomicroscopy and best-corrected visual acuity (BCVA) at all visits except the implant administration day visits, and gonioscopy at all visits except the implant administration day visits and the safety visits on the following day. The occurrence and severity of treatment-emergent adverse events (TEAEs), defined as adverse events with onset or worsening after implant administration, were based on the judgment of the investigator. CECD on specular microscopy was evaluated by the investigator using automated analysis at screening and every 4 months to inform study entry and clinical decision-making. Three high-quality scans of a central corneal location (< 25% of the image with shadows, overexposure, or blurring obscuring cell borders) were also captured for each eye and submitted to a reading center for centralized evaluation of CECD across sites. The average of the CECD in the three images was used for the analysis of CECD. Other safety assessments at selected visits included ophthalmoscopy, contact ultrasound pachymetry, and visual fields.

The primary efficacy endpoint was time to retreatment or rescue after the initial implant administration in the study eye, analyzed with the Kaplan–Meier method. Other efficacy endpoints included time to retreatment or rescue after the second implant administration in the study eye (analyzed with the Kaplan–Meier method) and IOP change from baseline by treatment cycle in study and implant-treated fellow eyes

that had not been retreated or rescued. Key safety measures included TEAEs and reading center evaluation of CECD.

2.6 Statistical Analysis

This interim analysis used data collected through 15 September 2023. The efficacy analyses used data after the first and second implant administrations in the study eye and data after the single implant administration in the fellow eye for the full analysis set (FAS) of all patients who received study treatment and had at least one postbaseline IOP assessment. Safety analyses used all available data for the safety analysis set of all patients who received at least one dose of study treatment.

Time to implant retreatment or rescue was analyzed using the Kaplan–Meier method. IOP values and change from baseline were summarized with descriptive statistics by visit and treatment cycle (cycle 1 after the initial implant administration and cycle 2 [study eyes only] after a second implant administration). To avoid confounding of efficacy data, IOP measurements taken after use of nonstudy (rescue) IOP-lowering treatment were excluded from analysis.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 and summarized with descriptive statistics. Analyses of reading center CECD values included mean CECD, percentage decrease in CECD from baseline, and proportion of eyes with a ≥ 20% decrease in CECD from baseline. A threshold of 20% was used in the categorical analysis because ±10% variations in CECD measurements are not reliable or clinically meaningful [27]. Analysis of ≥ 30% decreases in CECD from baseline, commonly used for other more invasive ocular glaucoma procedures [28], is also provided.

As there were no statistical hypotheses for the study, the sample size was determined empirically. Enrollment of approximately 425 patients receiving the 10-µg bimatoprost implant was planned to achieve a sufficient number of patients treated with multiple administrations of the implant.

3 Results

3.1 Patient Disposition and Study Treatment Exposure

The study completed enrollment with a total of 446 patients enrolled. At the time of the interim database lock, the majority of the patients (367 of 446, 82.3%) were ongoing in the study, 27 patients (6.1%) had completed the study, and 52 patients (11.7%) had discontinued from the study, most commonly because of patient withdrawal (Online Resource 3).

A total of 441 patients received at least one implant in the study eye and constituted the FAS used for analyses. Among patients in the FAS, 262 (59.4%) received only one implant in the study eye, 179 (40.6%) received a second implant in the study eye, and 176 (39.9%) received an implant in the fellow eye. The mean (standard deviation, SD) duration of follow-up after the first study eye administration was 427 (312) days (range, 2–1477) and after the second study eye administration was 332 (244) days (range, 2–1193). The mean total duration of implant exposure in the study eye for patients in the FAS was 614.0 (344.67) days (range, 2–1477), and 378 patients (85.7%) had at least 12 months of follow-up at the time of the interim database lock.

3.2 Baseline Characteristics of Patients and Implant-Treated Eyes (FAS)

Patients were typically White (81.6%) or Black or African American (15.0%), and the majority (54.2%) were female (Table 1). The mean age was 62.5 years (range, 26–88). The most common reasons for inadequate IOP control with topical medication in the study eye were memory loss (45.4% of patients) and intolerant/side effects of drop therapies (31.1% of patients) (Table 1).

Most of the study and fellow eyes treated with the bimatoprost implant were diagnosed with primary OAG, and most were phakic (Table 2). Although the majority of the implant-treated eyes had wide (Shaffer grade 4) inferior angles, > 40% had Shaffer grade 3 angles (Table 2).

3.3 Efficacy Outcomes

3.3.1 Duration of Effect

Kaplan–Meier analysis demonstrated a > 1-year duration of effect of the initial bimatoprost implant administration (cycle 1) in study eyes (Fig. 2). The median time (95% confidence interval, CI) from the first implant administration to requiring either a second implant administration or rescue treatment was 392 (369, 485) days, and the probability of not having required a second administration or rescue treatment was 57.5% at day 360 and 33.4% at day 720.

Repeat treatment with the bimatoprost implant similarly demonstrated a long duration of effect. In Kaplan–Meier analysis of time to retreatment or rescue after a second implant administration (cycle 2) in study eyes, the median time (95% CI) to requiring either a third implant administration or rescue treatment was 342 (296, 378) days. The probability of not having required a third administration or

Table 1 Baseline patient characteristics (FAS)

Parameter	Patients ($N = 441$)
Age, mean (SD), years	62.5 (10.89)
> 65, *n* (%)	184 (41.7)
Range	26–88
Sex, *n* (%)	
Female	239 (54.2)
Male	202 (45.8)
Race, *n* (%)	
White	360 (81.6)
Black or African American	66 (15.0)
Other or multiple races	15 (3.4)
Hispanic or Latino ethnicity, *n* (%)	50 (11.3)
Reason for inadequate IOP control with topical medication in study eye, *n* (%)[a]	
Memory loss	200 (45.4)
Intolerant/side effects of drop therapies	137 (31.1)
Physical inability to instill eye drops	29 (6.6)
Both memory loss and physical inability to instill drops	2 (0.5)
Other[b]	73 (16.6)
Required washout of IOP-lowering medication in study eye, *n* (%)	412 (93.4)
SOC treatment in fellow eye, *n* (%)	
PGA	248 (56.2)
Beta-blocker	106 (24.0)
Carbonic anhydrase inhibitor	32 (7.3)
Alpha-agonist	26 (5.9)
No medication	94 (21.3)

FAS full analysis set, *IOP* intraocular pressure, *PGA* prostaglandin analog/prostamide, *SD* standard deviation, *SOC* standard-of-care

[a]Investigators selected the reason(s) from options of "memory loss," "intolerant/side effects of drop therapies," "physical inability to instill eye drops," and "other" on the case report form.

[b]The most common "other" reasons were cost of medication and nonadherence or inconsistency with use of topical medications.

rescue treatment was 43.4% at 360 days and 16.5% at 720 days after the second implant administration.

3.3.2 IOP Reduction in Unrescued Eyes

After the day 1 bimatoprost implant administration, the mean (SD) reduction from baseline IOP in study eyes without retreatment or rescue was 8.3 (3.69) mmHg ($n = 409$) at week 12, 7.5 (3.71) mmHg ($n = 326$) at week 24, and 6.4 (3.75) mmHg ($n = 183$) at month 12 (Fig. 3). In eyes that received repeat treatment, the second implant administration resulted in similar IOP lowering at 12 weeks after administration. The mean (SD) reduction from baseline IOP in unrescued study eyes at week 12 in cycle 2 was 7.9 (4.02) mmHg ($n = 131$).

Among the 176 implant-treated fellow eyes, 91.5% received topical IOP-lowering medication SOC treatment before the implant administration. The medications used in SOC treatment were PGAs, beta-blockers, carbonic anhydrase inhibitors, and alpha-agonists in 68.8%, 23.3%, 9.7%, and 3.4% of eyes, respectively. Mean IOP at the last scheduled visit with available IOP data prior to the implant administration was 17.7 mmHg in the implant-treated fellow eyes. After withdrawal of the SOC treatment and administration of the implant, IOP in unrescued eyes was maintained at a similar level (Fig. 4).

3.4 Safety Outcomes

3.4.1 Adverse Events

The most common ocular TEAEs in study eyes were conjunctival hyperemia (cycle 1: 14.3% and cycle 2: 12.8%) known to be associated with the administration procedure and increased IOP (cycle 1: 9.5% and cycle 2: 12.3%), which can occur when the implant effect wears off (Table 3). Among the 441 study eyes, conjunctival hyperemia was reported as a TEAE in 77 (17.5%) eyes. The conjunctival hyperemia typically occurred within 2 days after an implant administration (52 eyes, 11.8%).

Table 2 Baseline characteristics of implant-treated study and fellow eyes (FAS)

Parameter	Study eyes ($N = 441$)	Fellow eyes ($N = 176$)
Diagnosis, *n* (%)		
OAG		
Primary	354 (80.3)	136 (77.3)
Pseudoexfoliation	6 (1.4)	2 (1.1)
Pigmentary	5 (1.1)	2 (1.1)
OHT	76 (17.2)	35 (19.9)
Inferior angle grade (Shaffer)		
3	202 (45.8)	75 (42.6)
4	239 (54.2)	101 (57.4)
Lens status, *n* (%)		
Phakic	352 (79.8)	145 (82.4)
Pseudophakic	89 (20.2)	31 (17.6)
IOP, mean (SD), mmHg	25.6 (2.99)	17.7 (4.21)[a]
CCT, mean (SD), µm	551.8 (32.59)	554.1 (35.14)
CECD, mean (SD), cells/mm^2	2445.4 (383.67)	2481.8 (383.74)[a]

CCT central corneal thickness, *CECD* central corneal endothelial cell density, *FAS* full analysis set, *IOP* intraocular pressure, *OAG* open-angle glaucoma, *OHT* ocular hypertension, *SD* standard deviation

[a]Baseline value for the fellow eye was defined as the last non-missing assessment before being treated with the bimatoprost implant. The fellow eye was generally receiving standard-of-care treatment at that time.

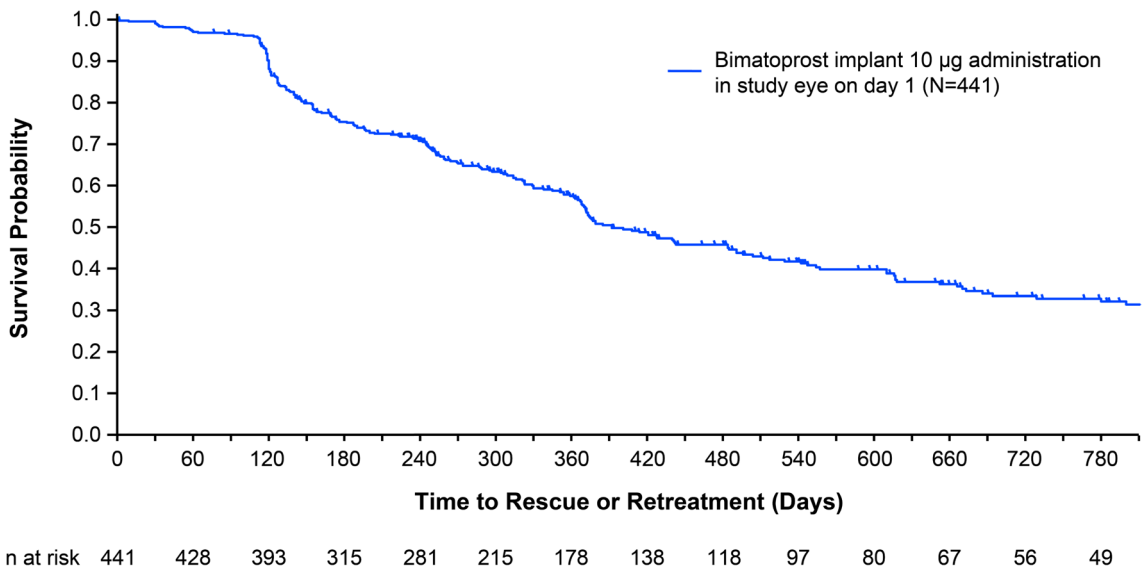

Fig. 2 Longevity of IOP management without retreatment or rescue after a single bimatoprost implant administration in the study eye. *IOP* intraocular pressure

The severity of conjunctival hyperemia was reported to be mild in 54 (12.2%) eyes, moderate in 22 (5.0%) eyes, and severe in 1 (0.2%) eye. The hyperemia that occurred was well-tolerated, with no patient dropping out of the study because of conjunctival hyperemia.

Corneal TEAEs, most commonly corneal endothelial cell loss (ECL) and corneal edema, were reported in 5.7% of study eyes in cycle 1 and 6.1% of study eyes in cycle 2 (Online Resource 4). The overall incidence of corneal TEAEs was 5.0% in eyes with Shaffer grade 4 angles compared with 13.9% in eyes with Shaffer grade 3 angles (Table 4). Three (0.7%) of the cycle 1 implants and two (1.1%) of the cycle 2 implants were removed because of

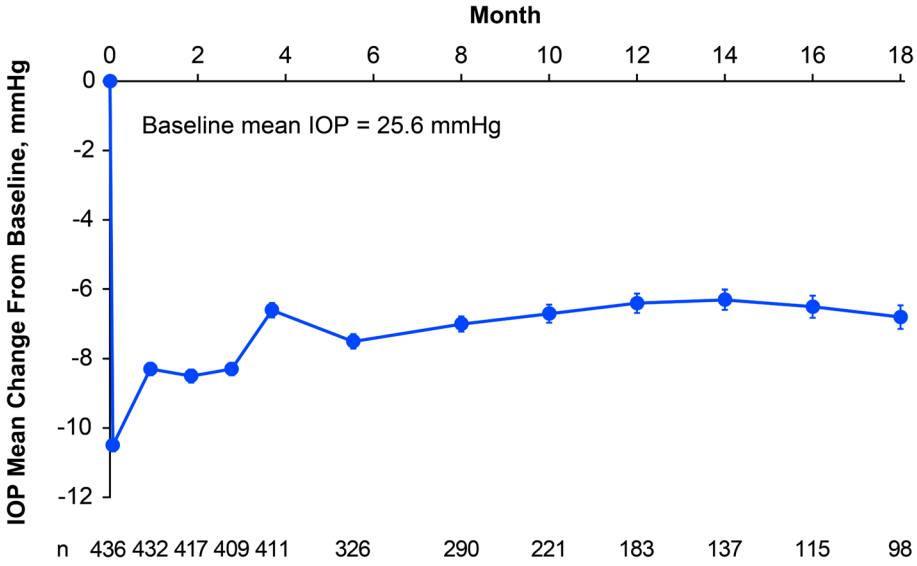

Fig. 3 Mean change in IOP from baseline in unrescued study eyes after a single bimatoprost implant administration. Error bars indicate the standard error of the mean. *IOP* intraocular pressure

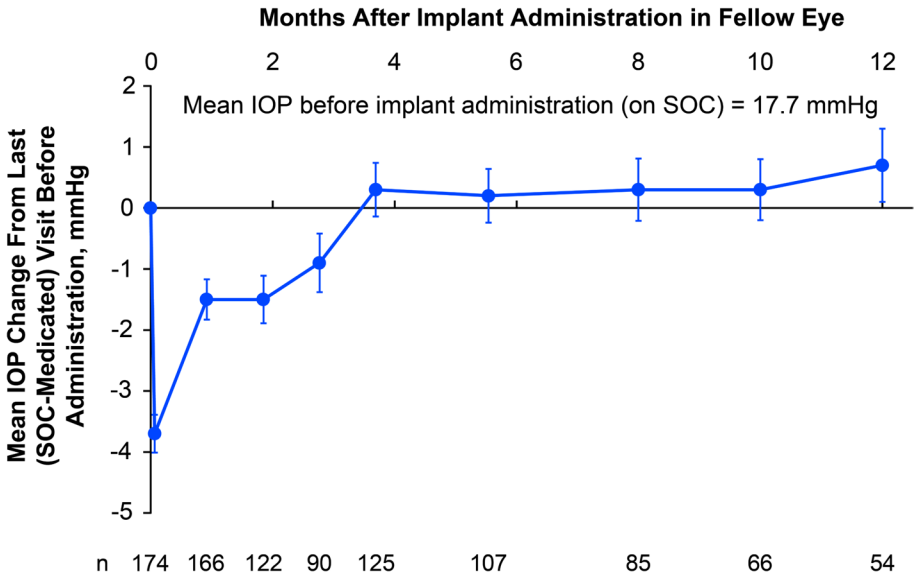

Fig. 4 Mean IOP change from the last visit (generally SOC-medicated) before a single implant administration in eligible fellow eyes. Fellow eyes received SOC treatment that was stopped at least 1 day before the implant administration. The baseline (time 0) measurement shown was the last non-missing assessment at a scheduled visit prior to the implant administration. Error bars indicate the standard error of the mean. *IOP* intraocular pressure, *SOC* standard-of-care

TEAEs (3 corneal edema, 1 corneal ECL, and 1 medical device removal after erroneous placement).

3.4.2 Corneal Endothelial Cell Density

Figure 5 shows the mean CECD over time in study eyes that received up to three administrations of the bimatoprost implant and fellow eyes that received a single implant administration. The mean percentage change from baseline in CECD in study eyes was −4.4% ($n = 265$) at month 12 and −7.5% ($n = 137$) at month 24. When CECD in study eyes was analyzed by cycle, the mean percentage change from baseline in CECD at 12 months after implant administration was −4.3% ($n = 201$) in cycle 1 and −8.5% ($n = 60$) in cycle 2. At 24 months after implant administration, the mean percentage change from baseline in CECD was −6.3% ($n = 64$) in cycle 1 and −16.2% ($n = 12$) in cycle 2. In the implant-treated fellow eyes, the mean percentage change from baseline in CECD after single administration was −2.7% ($n = 82$) at month 12 and −5.0% ($n = 38$) at month 24.

Decreases in CECD from baseline of ≥ 20% and ≥ 30% were observed in 10.0% and 6.0% of study eyes, respectively (Table 5). The incidence of ≥ 20% ECL was 5.4% in study eyes with wide (Shaffer grade 4) angles compared with 15.6% in those with Shaffer grade 3 angles (Table 5). A trend for a lower incidence of ≥ 20% ECL in pseudophakic study eyes (5.2%) compared with phakic study eyes (11.1%)

Table 3 Incidence of ocular TEAEs in bimatoprost implant–treated eyes

TEAE, *n* (%)	Study eye			Fellow eye
	Overall (*N* = 441)	Cycle 1 (*N* = 441)	Cycle 2 (*N* = 179)	(*N* = 176)
Any ocular TEAE	224 (50.8)	186 (42.2)	84 (46.9)	64 (36.4)
Conjunctival hyperemia	77 (17.5)	63 (14.3)	23 (12.8)	14 (8.0)
IOP increased	59 (13.4)	42 (9.5)	22 (12.3)	19 (10.8)
Corneal endothelial cell loss	31 (7.0)	18 (4.1)	9 (5.0)	8 (4.5)
Dry eye	28 (6.3)	20 (4.5)	9 (5.0)	10 (5.7)
Eye irritation	16 (3.6)	13 (2.9)	2 (1.1)	1 (0.6)
Eye pain	15 (3.4)	10 (2.3)	6 (3.4)	3 (1.7)
Cataract	14 (3.2)	9 (2.0)	4 (2.2)	3 (1.7)
Corneal edema	14 (3.2)	9 (2.0)	4 (2.2)	1 (0.6)

All TEAEs reported in ≥ 3% of study eyes are listed. The overall incidence includes TEAEs reported in cycle 3 after a third implant administration, so it can be more than the sum of the incidence in cycles 1 and 2

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

Table 4 Corneal TEAEs in study eyes stratified by Shaffer grade

TEAE, *n* (%)	Shaffer grade 3 (*N* = 202)	Shaffer grade 4 (*N* = 239)
Overall incidence of any corneal TEAE	28 (13.9)	12 (5.0)
Corneal endothelial cell loss	22 (10.9)	9 (3.8)
Corneal edema	12 (5.9)	2 (0.8)
Corneal touch	3 (1.5)	0
Corneal disorder	1 (0.5)	1 (0.4)
Corneal opacity	1 (0.5)	0

TEAE treatment-emergent adverse event

The analysis of corneal TEAEs included the terms corneal disorder, corneal edema, corneal endothelial cell loss, corneal opacity, corneal thinning, and corneal touch

was also evident (Table 5). Among implant-treated fellow eyes, the incidence of ≥ 20% ECL after single administration was 3.9% (6/155).

3.4.3 Visual Acuity and Visual Fields

BCVA remained within two lines of baseline in most implant-treated study and fellow eyes (Online Resource 5). The mean change in the visual field mean deviation from baseline in study eyes was − 0.18 dB at month 12 and − 0.40 dB at month 24 (Table 6).

3.4.4 Implant Biodegradation

Typically, the implant was very small or completely biodegraded by 12 months after administration. The cycle 1 implant was no longer visible or ≤ 25% of initial size

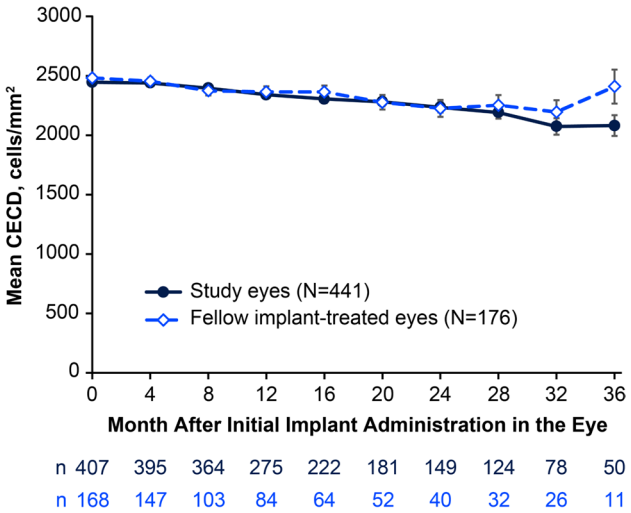

Fig. 5 Mean CECD over time in study eyes treated with a single or multiple implants and single implant-treated fellow eyes based on central reading center evaluation of specular microscopy. Error bars show the standard error of the mean. *CECD* central corneal endothelial cell density

in 66.3% and 94.3% of study eyes at months 12 and 24, respectively.

4 Discussion

In this interim analysis of the TRITON study, bimatoprost implant 10 µg demonstrated a long duration of effect after both the initial administration and a second PRN administration in the study eye. In study eyes that were not retreated or rescued, IOP lowering from untreated baseline was sustained over 18 months after a single implant administration.

Table 5 Rates of ≥ 20% and ≥ 30% endothelial cell loss in study eyes by cycle, Shaffer grade, and lens status

Eyes with loss in CECD from baseline, *n* (%)	Overall (*N* = 441)	Phakic (*N* = 352)	Pseudophakic (*N* = 89)	Cycle 1 (*N* = 441)	Cycle 2[a] (*N* = 179)
All study eyes	*N* = 402	*N* = 325	*N* = 77	*N* = 401	*N* = 140 or 142[b]
≥ 20% loss	40 (10.0)	36 (11.1)	4 (5.2)	24 (6.0)	12 (8.6)
≥ 30% loss	24 (6.0)	22 (6.8)	2 (2.6)	12 (3.0)	8 (5.6)
Shaffer grade 3	*N* = 179	*N* = 151	*N* = 28	*N* = 179	*N* = 64 or 65[c]
≥ 20% loss	28 (15.6)	26 (17.2)	2 (7.1)	13 (7.3)	11 (17.2)
≥ 30% loss	18 (10.1)	16 (10.6)	2 (7.1)	6 (3.4)	8 (12.3)
Shaffer grade 4	*N* = 223	*N* = 174	*N* = 49	*N* = 222	*N* = 76 or 77[d]
≥ 20% loss	12 (5.4)	10 (5.7)	2 (4.1)	11 (5.0)	1 (1.3)
≥ 30% loss	6 (2.7)	6 (3.4)	0	6 (2.7)	0

CECD central corneal endothelial cell density

[a]Eyes that had already demonstrated ≥ 20% (or ≥ 30%) CECD loss in cycle 1 were excluded from the analysis of eyes with 20% (or ≥ 30%) CECD loss in cycle 2.

[b]*N* was 140 for ≥ 20% loss and 142 for ≥ 30% loss.

[c]*N* was 64 for ≥ 20% loss and 65 for ≥ 30% loss.

[d]*N* was 76 for ≥ 20% loss and 77 for ≥ 30% loss.

In fellow eyes, a single implant administration replaced SOC treatment, and the IOP reduction from the SOC-treated baseline suggests that IOP was maintained over 12 months without use of eyedrops at a level similar to that provided by SOC therapy. The implant was generally well-tolerated and had an acceptable safety profile in eyes that received up to two administrations under a PRN readministration regimen.

In implant-treated study eyes, the median time to retreatment or rescue was approximately 13 months after the initial administration and 11 months after the second administration. These findings are consistent with literature reports of a long duration of IOP control with the implant. In a phase 1/2 study, 5 of the 21 enrolled patients (23.8%) with OAG who received a 10-µg dose strength of the bimatoprost implant required no additional IOP-lowering treatment for up to 2 years after a single administration [29]. At 2 years, the mean change from baseline IOP in the implant-treated eye of those 5 patients was − 7.4 mmHg [25]. In the ARTEMIS phase 3 studies, study eyes diagnosed with OAG or OHT received three implants at a fixed 16-week dosing interval, and in each study had a > 75% probability of not requiring any additional IOP-lowering treatment for 12 months after the third administration [21, 23]. In a prospective, 12-month, phase 3b study evaluating 24-hour IOP lowering after a single administration of the 10-µg bimatoprost implant in patients with OAG or OHT, 23 of the 31 enrolled patients (74.2%) did not require any rescue IOP-lowering treatment in the implant-treated eye for 12 months after the administration, and the mean change from baseline IOP in unrescued, implant-treated eyes was − 4.3 mmHg at month 12 [30].

Four retrospective, single-site, real-world studies have also provided evidence of the longevity of effect of the 10-µg bimatoprost implant [31–34]. In a case series of 46 eyes (38 patients) with OAG or OHT that received a single bimatoprost implant, 31 eyes (67.4%) did not require an IOP-lowering procedure or restarting of topical IOP-lowering medication over a mean period of 274 days follow-up [31]. Teymoorian et al. [32] reported a large case series of 197 eyes (105 patients) with OAG or OHT in which a single implant administration provided sustained mean IOP lowering for up to 1 year, with use of topical IOP-lowering medications reduced from baseline in the implant-treated eyes [32]. Sarkisian et al. [33] reported a similar large case

Table 6 Visual field MD changes from baseline on Humphrey perimetry in implant-treated eyes

	Study eye (*N* = 441)	Fellow eye (*N* = 176)
Baseline MD, mean (SE), dB	−2.19 (0.233) *n* = 388	−0.95 (0.293) *n* = 154
Mean (SE) change in MD from baseline, dB		
Week 24	−0.13 (0.176) *n* = 305	−0.39 (0.307) *n* = 119
Month 12	−0.18 (0.256) *n* = 255	−0.69 (0.454) *n* = 68
Month 18	−0.14 (0.231) *n* = 180	−0.33 (0.482) *n* = 49
Month 24	−0.40 (0.276) *n* = 135	−0.60 (0.506) *n* = 38
Month 30	−0.79 (0.343) *n* = 90	−0.64 (0.625) *n* = 25
Month 36	−0.01 (0.446) *n* = 47	−0.69 (0.735) *n* = 14

MD mean deviation

series in 197 eyes (105 patients) with OAG or OHT in which the mean IOP was reduced from baseline through 1 year after a single implant administration, and the mean number of topical IOP-lowering medications used was reduced from 1.4 at baseline to 0.2 at 11–13 months. Topical IOP-lowering medication use was also decreased after a single implant administration in another case series of 129 eyes (81 patients), most diagnosed with primary OAG [34]. In that study, implant-treated eyes had a 40.5% probability of not requiring any added IOP-lowering treatment through month 12 postadministration [34].

In vitro and in vivo data suggest that the bimatoprost implant releases drug for approximately 3–4 months [21, 35, 36]. A study in beagle dogs demonstrated that the implant achieves much higher drug concentrations in the iris–ciliary body target tissue for IOP lowering compared with topical dosing of bimatoprost [36]. In the dog study, intraocular bimatoprost levels were beneath the limit of quantitation at 4.2 months after implant administration [21], and similarly, in the ARTEMIS 1 clinical study, bimatoprost levels in aqueous humor samples taken from two patients were below the limit of quantitation (< 0.05 ng/mL) at 100 and 114 days after the last implant administration [21]. However, as seen in the current study and previous studies [21, 23, 25, 30], the effects of the implant on IOP typically last longer than the expected duration of drug release and intraocular drug bioavailability. As the mechanism of IOP lowering by PGAs including bimatoprost involves matrix metalloproteinase (MMP)-mediated remodeling of the extracellular matrix in outflow tissues, it has been suggested that the high concentrations of bimatoprost in target tissues after implant administration may produce enhanced upregulation of MMPs, leading to more durable tissue remodeling and sustained IOP lowering [21, 25, 37, 38]. In support of this hypothesis, in isolated ciliary muscle and trabecular cells, bimatoprost was shown to produce dramatic upregulation in MMP1 only at the high drug concentrations observed in bimatoprost implant–treated eyes [39].

Clinical studies have evaluated ECL after bimatoprost implant treatment with a single or multiple implants. In the ARTEMIS studies, ECL most commonly occurred after multiple implant administrations, likely because of slow implant biodegradation and accumulation of residual implants that physically interacted with and damaged the cornea [21, 23, 35]. In this study, study eyes were eligible for a PRN second administration of the bimatoprost implant only if at least 16 weeks had passed since the initial administration and the initial implant administered was < 25% of its original size. Under these conditions, both the initial administration and a single readministration of the implant had acceptable safety profiles. The results of this interim analysis of the TRITON study demonstrate that the bimatoprost implant can be safely readministered when the risk of accumulated residual implants is appropriately mitigated.

Importantly, this interim analysis showed that the incidence of corneal TEAEs and ≥ 20% ECL was reduced by > 60% in eyes with Shaffer grade 4 angles compared with eyes with Shaffer grade 3 angles. There was also a trend for reduced incidence of ≥ 20% ECL in pseudophakic eyes compared with phakic eyes. These results inform the selection of eyes for bimatoprost implant treatment and indicate that the safety profile of the initial implant administration and PRN readministration is most favorable in pseudophakic eyes with wide open (Shaffer grade 4) angles.

At the time of the interim database lock, the TRITON study was ongoing with large variation in the duration of participation and limited data at later timepoints. Therefore, the duration of effect of the implant may be more accurately estimated when the study is completed. Another limitation is that the study design does not include randomization or masking. Also, SOC therapy in treated fellow eyes, which for safety reasons could be continued until 1 day before implant administration, could have influenced IOP measurements at early timepoints after the administration. A study strength was that it evaluated the use of the bimatoprost implant in a more real-world clinical setting than the phase 3 studies, with physician determination of individual patient need for additional IOP-lowering treatment through retreatment or rescue. As the study is using PRN administration and the interim dataset includes extensive data on outcomes after a single implant administration, the interim results provide valuable information for physicians currently using the implant on label (a single implant per eye) in their practices.

5 Conclusions

In this analysis of interim data from the TRITON study, the bimatoprost implant provided a long duration of IOP management without use of IOP-lowering eyedrops after both the initial administration and a second PRN administration in the study eye. The results suggest that for patients with characteristics similar to those of the study population, IOP may be controlled without eye drops in one-third of implant-treated eyes for 2 years after a single implant administration. The safety profile of initial and single repeat administration was acceptable. Full results of the study will be reported at study completion.

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Declarations

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Conflict of interest Amanda K. Bicket is a consultant for W.L. Gore and Associates, Inc. Christian Brinkmann has received financial compensation from AbbVie, Afidera, Appelis, Bayer, Heidelberg Engineering, Novartis, Santen, Teleon Surgical, and Théa Laboratories. William C. Christie is a consultant for Allergan (an AbbVie company). Petrus N.J. Gous has no financial interests to disclose. Miriam Kolko is a speaker for AbbVie, Santen, Théa Laboratories, and Topcon; and sits on advisory boards for AbbVie, Santen, and Théa Laboratories. Jan Luebke is a speaker for AbbVie, Alcon, Glaukos, iStar Medical, Santen, and Théa Laboratories and sits on advisory boards for AbbVie and Santen. Francesco Oddone is a speaker for AbbVie, Omikron Italia, Santen, Sifi, and Theà; sits on advisory boards for AbbVie, Dompè, and Santen; and has received research grants from AbbVie, Santen, and Omikron Italia. Steven M. Silverstein has no disclosures beyond participation in this clinical study. Marina Bejanian, E. Randy Craven, Jenny Jiao, Jyotsna Maram, Ashley Nguyen, Yongjia Pu, and Michael R. Robinson 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 NCT03850782).

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

Data availability 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), as long as 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 (SAP), and execution of a data sharing agreement (DSA). 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.

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