AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Latanoprostene Bunod 0.024% versus Timolol Maleate 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension

The APOLLO Study

Robert N. Weinreb, MD,[1] *Baldo Scassellati Sforzolini, PhD,*[2] *Jason Vittitow, PhD,*[2] *Jeffrey Liebmann, MD*[3]

Purpose: To compare the diurnal intraocular pressure (IOP)-lowering effect of latanoprostene bunod (LBN) ophthalmic solution 0.024% every evening (qPM) with timolol maleate 0.5% twice daily (BID) in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Design: Phase 3, randomized, controlled, multicenter, double-masked, parallel-group clinical study.

Participants: Subjects aged ≥18 years with a diagnosis of OAG or OHT in 1 or both eyes.

Methods: Subjects were randomized (2:1) to a 3-month regimen of LBN 0.024% qPM or timolol 0.5% 1 drop BID. Intraocular pressure was measured at 8 AM, 12 PM, and 4 PM of each postrandomization visit (week 2, week 6, and month 3). Adverse events were recorded throughout the study.

Main Outcome Measures: The primary efficacy end point was IOP in the study eye measured at each of the 9 assessment time points. Secondary efficacy end points included the proportion of subjects with IOP ≤18 mmHg consistently at all 9 time points and the proportion of subjects with IOP reduction ≥25% consistently at all 9 time points.

Results: Of 420 subjects randomized, 387 completed the study (LBN 0.024%, n = 264; timolol 0.5%, n = 123). At all 9 time points, the mean IOP in the study eye was significantly lower in the LBN 0.024% group than in the timolol 0.5% group ($P \leq 0.002$). At all 9 time points, the percentage of subjects with mean IOP ≤18 mmHg and the percentage with IOP reduction ≥25% were significantly higher in the LBN 0.024% group versus the timolol 0.5% group (mean IOP ≤18 mmHg: 22.9% vs. 11.3%, $P = 0.005$; IOP reduction ≥25%: 34.9% vs. 19.5%, $P = 0.001$). Adverse events were similar in both treatment groups.

Conclusions: In this phase 3 study, LBN 0.024% qPM demonstrated significantly greater IOP lowering than timolol 0.5% BID throughout the day over 3 months of treatment. Latanoprostene bunod 0.024% was effective and safe in these adults with OAG or OHT. *Ophthalmology 2016;123:965-973 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Open-angle glaucoma (OAG) is the leading cause of irreversible blindness and affects tens of millions of individuals worldwide.[1,2] It is associated with progressive visual field damage and visual function loss with detrimental effects on health-related quality of life, even in early stages of the disease.[3] Elevated intraocular pressure (IOP) is a major risk factor for primary OAG,[4,5] and its reduction has been shown to delay or reduce the risk of glaucoma development in ocular hypertensive individuals[5] and slow disease progression in patients with OAG.[6–11] Pharmacologic lowering of IOP is the first-line intervention in most individuals with elevated IOP with or without glaucomatous optic neuropathy (OAG and ocular hypertension [OHT], respectively), and initial therapy is typically with a topical prostaglandin analog.[12] However, many patients will require more than 1 therapy to achieve target IOP.[12]

Latanoprostene bunod (LBN, BOL-303259-X) is a novel nitric oxide (NO)-donating prostanoid FP receptor agonist that is rapidly metabolized in the eye into latanoprost acid, an F2α prostaglandin analog, and butanediol mononitrate. Nitric oxide is subsequently released from butanediol mononitrate in conjunction with 1,4 butanediol, an inactive metabolite.[13,14] Latanoprost acid reduces IOP by increasing aqueous humor outflow primarily through the uveoscleral pathway ("nonconventional" route) via long-term remodeling of the extracellular matrices in the ciliary body.[15–18] In contrast, NO donors reduce IOP primarily by causing relaxation of the trabecular meshwork and Schlemm's canal, resulting in increased aqueous humor outflow ("conventional drainage" routes).[19–27]

Latanoprostene bunod demonstrated IOP-lowering activity in several preclinical models of OHT, including in rabbits that are known to be insensitive to latanoprost, demonstrating the contribution of NO to the IOP-lowering effect of LBN.[13] Further, a well-controlled phase 2 study in 413 patients with OAG or OHT demonstrated a

© 2016 by the American Academy of Ophthalmology
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Published by Elsevier Inc.

http://dx.doi.org/10.1016/j.ophtha.2016.01.019
ISSN 0161-6420/16

significantly greater reduction in mean diurnal IOP after 28 days of treatment with LBN 0.024% compared with latanoprost 0.005%.[14] The current study was designed to compare the diurnal IOP-lowering effect of LBN ophthalmic solution 0.024% every evening (qPM) (hereafter referred to as "LBN 0.024%") with timolol maleate ophthalmic solution 0.5% twice daily (BID) (hereafter referred to as "timolol 0.5%") in subjects with OAG or OHT.

Methods

Study Objectives and Design

The APOLLO study (Clinicaltrials.gov identifier: NCT01749904) was a phase 3, randomized, multicenter, double-masked, parallel-group clinical study. The study was composed of 2 phases: an active-controlled 3-month efficacy phase followed by an open-label 9-month safety extension phase. The primary objective of the efficacy phase was to evaluate the noninferiority of LBN 0.024% qPM compared with timolol 0.5% BID with regard to mean IOP reduction at each time point throughout the 3 months of treatment. If LBN 0.024% qPM was determined to be noninferior to timolol 0.5% BID, the secondary objective was to assess the superiority of LBN 0.024% qPM to timolol 0.5% BID. We report results from the efficacy phase of the study; data from the 9-month open-label extension phase will be reported separately. Institutional Review Board/Ethics Committee approval was obtained at each participating site.

The study was conducted at 45 investigational sites in the United States and Europe and was performed in accordance with Good Clinical Practices (as described by the International Conference on Harmonisation), the Code of Federal Regulations, the ethical principles in the Declaration of Helsinki, Health Insurance Portability and Accountability Act regulations, and other applicable local regulations. All subjects provided written informed consent before the performance of any study procedures.

Subjects

The study enrolled men and women aged ≥18 years with a diagnosis of OAG (including pigmentary or pseudoexfoliative OAG) or OHT in 1 or both eyes. Intraocular pressure was assessed once at screening and at 8 AM, 12 PM, and 4 PM at baseline to establish eligibility and baseline values. Eligible subjects had an IOP ≥26 mmHg at a minimum of 1 time point, ≥24 mmHg at a minimum of 1 time point, and ≥22 mmHg at 1 time point in the same eye, and IOP ≤36 mmHg at all 3 measurement time points in both eyes at baseline, which occurred after a washout period in those subjects receiving topical hypotensive treatment at the time of enrollment. In addition, subjects were required to have a best-corrected visual acuity (BCVA) of +0.7 logarithm of the minimum angle of resolution (logMAR) units (Snellen equivalent of ~20/100) or better in either eye.

Subjects were excluded if they had participated in any clinical trial within 30 days before screening for subjects requiring a washout period or 30 days before baseline (day 0) for subjects not requiring a washout period. Additional exclusion criteria included a known hypersensitivity or contraindications to latanoprost, NO-donating medications, timolol maleate, other β-adrenergic receptor antagonists, or any ingredients in study drugs; central corneal thickness >600 μm in either eye; any condition that prevented reliable applanation tonometry (e.g., significant corneal surface abnormalities) in either eye; and advanced glaucoma (cup-to-disk ratio >0.8 or split fixation) or other significant ophthalmic disease. Subjects requiring treatment with ocular or systemic corticosteroids, or who had an anticipated need to initiate or modify medication that was known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers) during the efficacy phase also were excluded from study participation.

Study Treatments and Assessments

Baseline data, including demographics, relevant medical and ocular history, and concomitant medications, were recorded at the screening visit. Eligible subjects receiving topical ocular hypotensive treatment at screening were required to discontinue treatment and undergo a washout period before the baseline visit (day 0), varying in duration depending on the IOP-lowering medication used (a minimum of 5 days for miotics and oral/topical carbonic anhydrase inhibitors, 14 days for α and α/β agonists, and 28 days for prostaglandin analogs, β-blockers, and combination drugs including β-blockers). Subjects taking topical β-blockers or prostaglandin analogs at screening were required to participate in a midwashout safety evaluation visit (day −14). Subjects were withdrawn from the study if their IOP was >36 mmHg in either eye at any point during the washout period.

After baseline IOP measurements, eligible subjects were randomized 2:1 to receive LBN 0.024% qPM and vehicle every morning or timolol 0.5% BID for 3 months. For masking purposes, each treatment was labeled with identical investigational labels and packaged in identical kit boxes. Study drug was dispensed via an Interactive Response Technology system. Randomization schedules were created by a designated unmasked statistician using SAS Version 9.2 (SAS Institute, Inc., Cary, NC). Each subject received study kits containing 4 eye drop bottles and was instructed to instill 1 drop of the study drug from the "night" dosing bottle in the affected eye(s) at approximately 8 PM each day and 1 drop of the study drug from the "day" dosing bottle at approximately 8 AM each day (with the exception of the morning of scheduled clinic visits, when the subject instilled the study drug after 8 AM in-clinic assessments).

The study eye was the eye that qualified per inclusion criteria on day 0; if both eyes qualified, then the study eye was the eye with the higher mean diurnal IOP value at day 0 or the right eye if both eyes had the same mean diurnal IOP value. If both eyes of a subject had a diagnosis of OAG or OHT, then both eyes were treated for the duration of the study, even if only 1 eye qualified at day 0.

After randomization, subjects completed 3 study visits: week 2 (±2 days), week 6 (±3 days), and month 3 (±10 days). At each visit, IOP was measured in both eyes at 8 AM, 12 PM, and 4 PM using a Goldmann applanation tonometer. Whenever possible, the same operator measured IOP, and the same tonometer was used at each visit for a given subject.

Safety assessments included adverse events, vital signs, BCVA (measured using the Early Treatment Diabetic Retinopathy Study standard protocol), conjunctival hyperemia assessment, slit-lamp examination findings, ophthalmoscopy findings, and specular microscopy. The investigator graded conjunctival hyperemia on a scale of 1 to 4 using photographic standards (1 = none, 4 = severe). Slit-lamp findings, ophthalmoscopy findings, and specular microscopy results will be reported separately along with data from the 9-month open-label extension phase.

End Points

The primary efficacy end point was the IOP in the subject's study eye measured at 8 AM, 12 PM, and 4 PM at each postbaseline visit (week 2, week 6, and month 3). The key secondary efficacy end points were the proportion of subjects with IOP ≤18 mmHg

consistently at all 9 time points in the first 3 months and the proportion of subjects with IOP reduction ≥25% consistently at all 9 time points in the first 3 months. Additional secondary end points included the change from baseline (CFB) in IOP measured at 8 AM, 12 PM, and 4 PM at each postbaseline visit and the CFB in diurnal IOP (defined as the mean of IOP at 8 AM, 12 PM, and 4 PM) at each postrandomization visit. Safety end points during the efficacy phase included BCVA, conjunctival hyperemia assessment, and incidence of ocular and systemic adverse events.

Statistical Analysis

The sample size estimate was based on a noninferiority test of the difference between LBN 0.024% versus timolol 0.5% with respect to IOP in the per-protocol (PP) population, assuming a standard deviation (SD) of 3.75 mmHg, a power of 90%, a 2-sided $\alpha = 0.05$, and a noninferiority margin of 1.5 mmHg. The SD was based on data from a phase 2b study of LBN 0.024% and the timolol arm of a phase 3 study.[28] To account for potential dropouts and protocol violations, 393 subjects were to be randomized to the LBN 0.024% and timolol 0.5% treatment groups in a 2:1 ratio.

The primary efficacy analysis was performed using analysis of covariance (ANCOVA) in the intent-to-treat (ITT) population, which comprised all randomized subjects who instilled at least 1 dose of study drug and had at least 1 postbaseline IOP assessment. In the ANCOVA model, treatment was a variable and time-matched baseline mean IOP was a covariate. Missing data were inputted using the last observation carried forward (LOCF) method. The 2 treatment groups were compared for each time point by visit, and the least squares mean of each treatment group, the difference in the least squares mean (LBN 0.024%−timolol 0.5%), and the 2-sided 95% confidence interval (CI) for the difference were obtained. Noninferiority was determined if the upper limit of the CIs for the difference did not exceed 1.5 mmHg at all 9 time points and did not exceed 1.00 mmHg for ≥5 of the 9 time points. If noninferiority was determined, superiority at each time point was demonstrated if the upper limit of the 95% CI did not exceed 0 mmHg at all 9 time points. To supplement the primary analyses, the ANCOVA was repeated for the PP population (i.e., all subjects in the ITT population who remained in the study through month 3 with no missing postbaseline IOP assessments and no major protocol violations). In addition, the primary analysis was repeated on the ITT population using the worst observation carried forward (WOCF) method.

If noninferiority of LBN 0.024% to timolol 0.5% was shown, secondary end points analyzed were based on the ITT population with LOCF, with supportive analyses performed using the PP population. The proportion of subjects with IOP ≤18 mmHg at all time points in the first 3 months and the proportion with IOP reduction ≥25% at all time points in the first 3 months were summarized categorically. Percent reduction from baseline was calculated as 100*(baseline mean IOP − postbaseline mean IOP)/baseline mean IOP. For each key secondary end point, the 2-sided 95% CI around the difference in proportions (LBN 0.024%−timolol 0.5%) was calculated, and the *P* value was determined using Pearson's chi-square test. An ANCOVA of CFB in IOP was performed with fixed-effect terms for treatment and baseline for the specified postbaseline time points at week 2, week 6, and month 3. In addition, an ANCOVA of CFB in mean diurnal IOP was performed with fixed-effect terms for treatment and diurnal baseline IOP at each postbaseline visit. The CFB in IOP was summarized using descriptive statistics, and within-treatment group paired *t* tests were performed for the CFB mean IOP at each time point of each visit.

Safety analyses were based on the safety population, which included all randomized subjects who instilled at least 1 dose of the study drug. Ocular treatment-emergent adverse events (TEAEs) were summarized for study eyes, treated fellow eyes, and nontreated fellow eyes separately by treatment group. Nonocular (systemic) TEAEs were summarized using discrete summaries at the subject and event level, respectively, using the Medical Dictionary for Regulatory Activities coding of the system organ class and preferred term for each treatment group. Treatment-emergent adverse events were summarized by relationship to study drug and severity. Systolic and diastolic blood pressure and heart rate were summarized by visit using descriptive statistics. Other safety data presented in this article, including BCVA and conjunctival hyperemia, were described separately for study eyes, treated fellow eyes, and nontreated fellow eyes and summarized using descriptive statistics (BCVA) or categorically (conjunctival hyperemia).

All CIs, statistical tests, and *P* values were reported as 2-sided and assessed at the 5% significance level. Continuous data were summarized using descriptive statistics (number, mean, SD, median, minimum, and maximum). All statistical analyses were performed using SAS software (SAS Institute, Inc.) version 9.2 or higher.

Results

Subjects

Subjects were enrolled from January 31, 2013, to April 30, 2014. Of 679 subjects screened, 420 were randomized to treatment with LBN 0.024% (n = 286) or timolol 0.5% (n = 134). A total of 418 randomized subjects instilled at least 1 dose of study drug and comprised the safety population (n = 283 LBN 0.024%, n = 135 timolol 0.5%); 1 subject did not have any recorded postbaseline IOP readings; thus, 417 subjects were included in the ITT population (n = 284 LBN 0.024%, n = 133 timolol 0.5%). One subject randomized to LBN received timolol and therefore was included in the timolol 0.5% safety population and the LBN 0.024% ITT population. The PP population included 272 subjects (n = 192 LBN 0.024%, n = 80 timolol 0.5%). Overall, 387 subjects (92.6%) in the safety population (92.9% [263/283] of the LBN 0.024% group, 91.9% [124/135] of the timolol 0.5% group) and 387 subjects (92.8%) in the ITT population (93.0% [264/284] of the LBN 0.024% group, 92.5% [123/133] of the timolol 0.5% group) completed the 3-month treatment. For the 30 subjects in the ITT population who discontinued the study (n = 20 LBN 0.024%, n = 10 timolol 0.5%), reasons for discontinuation included adverse events (n = 4 in each group), withdrawal of consent (n = 6 LBN 0.024%, n = 1 timolol 0.05%), failure to follow required study procedures (n = 2 in each group), investigator decision (n = 1 LBN 0.024%, n = 2 timolol 0.5%), lost to follow-up (n = 1 LBN 0.024%), and other reasons (n = 6 LBN 0.024%, n = 1 timolol 0.5%).

Subjects in the ITT population had a mean age of 64.2 years, were of predominantly European or African ancestry, and were of non-Hispanic/non-Latino ethnicity. Treatment groups were comparable with regard to demographics (Table 1) and baseline eye characteristics (Table 2). More than two thirds of subjects (71.9%) were taking topical IOP-lowering medication at screening or had used IOP-lowering medication 30 days before screening and participated in a medication washout.

Efficacy

Primary Efficacy Outcomes. Mean IOP in the study eye was significantly lower in the LBN 0.024% group (range, 17.8−18.7 mmHg) than in the timolol 0.5% group (range, 19.1−19.8 mmHg) at all 9 efficacy time points assessed (8 AM, 12 PM, and 4 PM at

Table 1. Subject Demographics (Intent-to-Treat Population)

	LBN 0.024% (n = 284)	Timolol 0.5% (n = 133)	Total (N = 417)
Age, yrs			
Mean (SD)	64.7 (10.3)	63.1 (11.2)	64.2 (10.6)
Median (min, max)	65.0 (22, 88)	64.0 (23, 83)	65.0 (22, 88)
Age group, n (%)			
<65 yrs	138 (48.6)	67 (50.4)	205 (49.2)
≥65 yrs	146 (51.4)	66 (49.6)	212 (50.8)
Gender, n (%)			
Male	118 (41.5)	56 (42.1)	174 (41.7)
Female	166 (58.5)	77 (57.9)	243 (58.3)
Race, n (%)			
White	217 (76.4)	108 (81.2)	325 (77.9)
Black or African American	64 (22.5)	24 (18.0)	88 (21.1)
Asian	1 (0.4)	1 (0.8)	2 (0.5)
Other	2 (0.7)	0	2 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	30 (10.6)	13 (9.8)	43 (10.3)
Non-Hispanic and non-Latino	254 (89.4)	120 (90.2)	374 (89.7)

LBN = latanoprostene bunod; SD = standard deviation.

week 2, week 6, and month 3) (Fig 1). Noninferiority of LBN 0.024% to timolol 0.5% in the ITT population was demonstrated on the basis of ANCOVA for the comparison of mean IOP between treatment groups: The upper limit of the 95% CIs for the difference between treatments was ≤1.0 mmHg for all of the 9 efficacy time points (Table 3). Likewise, ANCOVA results demonstrated the superiority of LBN 0.024% to timolol 0.5% in the ITT population because the upper limit of the 95% CIs for the difference between treatments was ≤0 mmHg at all 9 time points (Table 3). The primary end point findings were supported by results of an ANCOVA analysis in the PP population and with WOCF in the ITT population (data not shown). Furthermore, primary end point findings were not affected by prior treatment status (subjects on treatment at enrollment vs. subjects not on treatment at enrollment), subject age (<65 vs. ≥65 years), or concurrent use of systemic β-blockers (data not shown).

Table 2. Baseline Eye Characteristics (Study Eyes, Intent-to-Treat Population)

	LBN 0.024% (n = 284)	Timolol 0.5% (n = 133)
Mean (SD) diurnal IOP, mmHg	26.7 (2.5)	26.5 (2.4)
Corneal thickness, μm		
Mean (SD)	546.3 (31.7)	549.6 (31.1)
Median	548.7	550.7
Range	409.0–598.7	461.0–597.0
Sphere (D)		
Mean (SD)	−0.45 (2.57)	−0.76 (2.63)
Median	0.00	−0.25
Range	−18.00 to 5.50	−12.25 to 4.25
Cylinder (D)		
Mean (SD)	0.13 (1.05)	0.25 (1.06)
Median	0.00	0.25
Range	−5.50 to 3.25	−3.00 to 4.00

D = diopters; IOP = intraocular pressure; LBN = latanoprostene bunod; SD = standard deviation.

Secondary Efficacy Outcomes. A higher percentage of subjects in the LBN 0.024% group (22.9%) compared with the timolol 0.5% group (11.3%) had an IOP ≤18 mmHg consistently at all 9 efficacy time points measured (Fig 2) (difference, 11.6%; 95% CI, 4.3–18.9; $P = 0.005$). Likewise, a higher percentage of subjects in the LBN 0.024% group (34.9%) compared with the timolol 0.5% group (19.5%) had an IOP reduction ≥25% consistently at all 9 time points measured (Fig 2) (difference, 15.3%; 95% CI, 6.6–24.0; $P = 0.001$). Similar results were observed in the PP population.

Further ANCOVA analysis showed that the mean CFB in mean IOP was greater in the LBN 0.024% group (range, −7.7 to −9.1 mmHg) than in the timolol 0.5% group (range, −6.6 to −8.0 mmHg) at all 9 efficacy time points (Fig 3). The difference in the CFB in mean IOP between treatment groups was statistically significant at all 9 efficacy time points ($P \leq 0.002$). As was the case for the individual time points, mean diurnal IOP (average of IOP at 8 AM, 12 PM, and 4 PM) was significantly lower in the LBN 0.024% group compared with the timolol 0.5% group at each visit (18.2 vs. 19.5 mmHg at week 2, 18.1 vs. 19.3 mmHg at week 6, and 18.2 vs. 19.4 mmHg at month 3; $P < 0.001$ for all). Similar to the CFB at individual time points, at each study visit, there was a statistically significantly ($P < 0.001$) greater CFB in mean diurnal IOP in the LBN 0.024% group (range, −8.4 to −8.6 mmHg) than in the timolol 0.5% group (range, −7.1 to −7.3 mmHg).

Safety

Exposure. Mean ± SD days of exposure to study drug in the safety population was similar in the LBN 0.024% group (89.7±14.4 days) and the timolol 0.5% group (89.4±18.4 days) during the 3-month efficacy phase.

Ocular Adverse Events. The percentage of study or fellow treated eyes experiencing at least 1 ocular TEAE was comparable in the LBN 0.024% and timolol 0.5% groups (Table 4). Ocular TEAEs reported in ≥1% of eyes in both treatment groups included eye irritation, conjunctival hyperemia, eye pain, dry eye, and instillation site pain. Most ocular TEAEs were considered related to the study drug and mild or moderate in severity with a few exceptions. In the LBN 0.024% group, 2 subjects experienced a severe TEAE in treated fellow eyes, scleritis and foreign body requiring surgery, both considered unrelated to treatment. One subject in the timolol 0.5% group had severe eye pain (study and fellow treated eye) and instillation site pain (study eye) considered possibly related to treatment, and 1 subject experienced a severe IOP increase considered unrelated study treatment.

Two subjects in the LBN treatment group discontinued because of ocular adverse events; 1 subject had mild conjunctival edema and mild conjunctival irritation, considered probably treatment related, in both eyes, and the other had severe scleritis in the treated fellow eye considered unrelated to study treatment. In the timolol group, 5 subjects discontinued because of an ocular adverse event. These included eyelid edema (mild, probably related), eye irritation (moderate, definitely related), eye allergy (moderate, unlikely related), and allergic conjunctivitis (moderate, unrelated) in both eyes of 4 subjects; and elevated IOP (severe, unrelated) in the treated fellow eye of 1 subject.

Nonocular Adverse Events. The proportion of subjects experiencing ≥1 nonocular TEAE was comparable in the LBN 0.024% and timolol 0.5% groups (12.7% and 14.1%, respectively). Treatment-related nonocular TEAEs were reported by 5 subjects (1.8%) in the LBN 0.024% group (headache in 2 subjects; fatigue

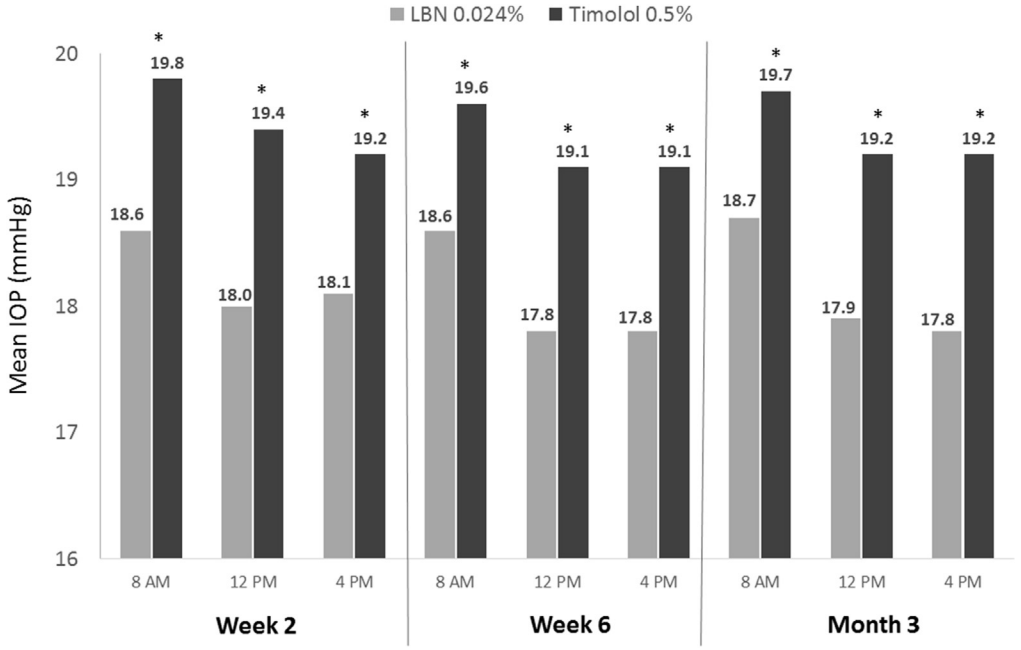

Figure 1. Mean intraocular pressure (IOP) (mmHg) in the study eye by visit, time point, and treatment group (intent-to-treat [ITT] population with last observation carried forward [LOCF]). Mean was the least squares mean of the mean IOP. LBN = latanoprostene bunod. *$P \leq 0.002$ versus timolol at the same assessment point.

in 1 subject; sinus congestion in 1 subject; hair color changes and hair disorder in 1 subject) and 3 subjects (2.2%) in the timolol 0.5% group (bradycardia, procedural headache, and rhinorrhea, each in 1 subject). Severe/serious nonocular TEAEs were experienced by 5 subjects in the LBN 0.024% group (femoral neck fracture, surgery for osteoarthritis, dizziness, chest pain, each in 1 subject; peripheral edema and pain in extremity in 1 subject) and by 2 subjects in the timolol 0.5% group (torn rotator cuff, arthropod bite). All severe/serious TEAEs were considered to be unrelated or unlikely related to the study drug; all other TEAEs were mild or moderate in severity. No deaths occurred during the 3-month treatment period.

Two subjects in the LBN treatment group discontinued because of a nonocular adverse event: severe dizziness considered unlikely to be related to treatment in 1 subject and moderate fatigue considered possibly related to treatment in the other.

Other Safety Measures. Mean vital sign measures (systolic blood pressure, diastolic blood pressure, and pulse rate) were similar between treatment groups, and no treatment-related trends were observed. In addition, mean logMAR BCVA values did not

Table 3. Primary End Point: Mean Intraocular Pressure in the Study Eye (Intent-to-Treat Population, Analysis of Covariance with Last Observation Carried Forward)

	Week 2			Week 6			Month 3		
	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM	8 AM	12 PM	4 PM
LBN 0.024% (n = 284)									
N	282	282	281	283	283	284	283	283	284
Mean IOP, mmHg*	18.6	18.0	18.1	18.6	17.8	17.8	18.7	17.9	17.8
Timolol 0.5% (n = 133)									
N	133	131	131	133	131	131	133	131	131
Mean IOP, mmHg*	19.8	19.4	19.2	19.6	19.1	19.1	19.7	19.2	19.2
Treatment difference†									
Adjusted mean IOP‡	−1.2	−1.4	−1.1	−1.0	−1.3	−1.3	−1.0	−1.3	−1.3
Upper 95% CI‡	−0.5	−0.7	−0.5	−0.4	−0.6	−0.6	−0.4	−0.6	−0.6
Lower 95% CI‡	−1.9	−2.1	−1.8	−1.7	−1.9	−2.0	−1.7	−1.9	−2.0
P value‡	<0.001	<0.001	<0.001	0.002	<0.001	<0.001	0.002	<0.001	<0.001

CI = confidence interval; IOP = intraocular pressure; LBN = latanoprostene bunod.
*Mean was the least squares mean of the mean IOP for the corresponding time point and visit at time-matched overall average baseline under ANCOVA.
†Treatment difference = LBN 0.024% − timolol 0.5%.
‡Adjusted mean, 95% CIs, and *P* values were from an ANCOVA model with treatment as a classification variable and time-matched baseline mean IOP as a covariate.

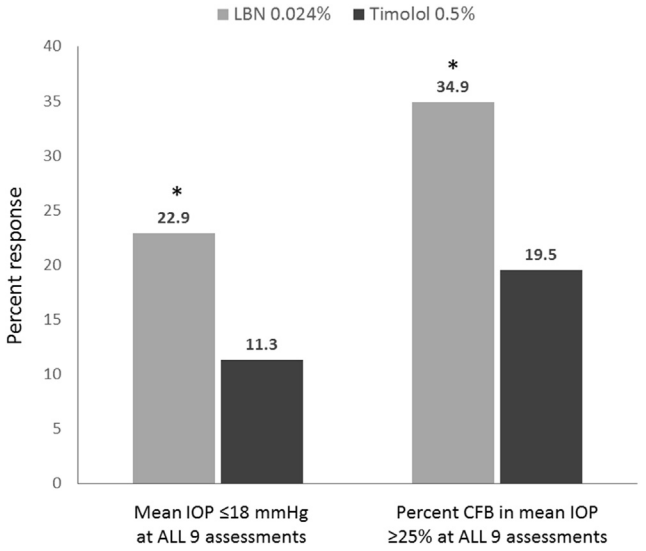

Figure 2. Response rates for key secondary efficacy end points after 3 months of treatment with latanoprostene bunod (LBN) 0.024% or timolol 05% (intent-to-treat [ITT] population with last observation carried forward [LOCF]). CFB = change from baseline; IOP = intraocular pressure. *$P \leq$ 0.005 versus timolol.

vary notably during the study. Mean (SD) logMAR BCVA in the study eye in the LBN and timolol treatment groups was 0.09 (0.137) and 0.07 (0.124) at baseline and 0.08 (0.134) and 0.07 (0.139) at 3 months, respectively.

Approximately 40% of subjects were observed by the investigator to have conjunctival hyperemia, mostly mild, at baseline before treatment, in their prospective evaluation of hyperemia using photographic standards. The percentage of subjects with conjunctival hyperemia was similar between posttreatment study visits and between the 2 treatment groups for both the study eyes and the treated fellow eyes with small variations from baseline in the overall incidence of conjunctival hyperemia through 3 months. However, the percentage of subjects with moderate or severe hyperemia was numerically higher in the LBN 0.024% group compared with the timolol 0.5% group in both study eyes and treated fellow eyes at week 2 (study eye: 9.6% and 0.7%, respectively; treated fellow eye: 10.2% and 1.5%, respectively), week 6 (study eye: 11.8% and 3.8%, respectively; treated fellow eye: 10.7% and 5.4%, respectively), and month 3 (study eye: 8.5% and 2.4%, respectively; treated fellow eye: 9.8% and 1.6%, respectively).

Discussion

This randomized, multicenter, double-masked parallel-group study demonstrated that LBN 0.024% instilled qPM resulted in significantly greater IOP lowering compared with timolol 0.5% instilled BID throughout the day over 3 months of treatment. The mean IOP in the study eye was statistically significantly lower in the LBN group than in the timolol group consistently at all 9 measured time points, whether analyzed for the ITT population using the LOCF or WOCF, supporting the robustness of the findings. Of note, the difference between the LBN and timolol groups in mean IOP exceeded 1 mmHg at all time points. The clinical significance of this difference is underscored by results of the Early Manifest Glaucoma Trial, which found that in patients with OAG, each millimeter of mercury of IOP reduction from baseline at the first follow-up visit (3 months) was associated with an approximately 10% reduction in progression of visual field loss.[9] More recently, Heijl[29] suggested a 19% reduction in the risk of visual field progression for every 1 mmHg IOP reduction on the basis

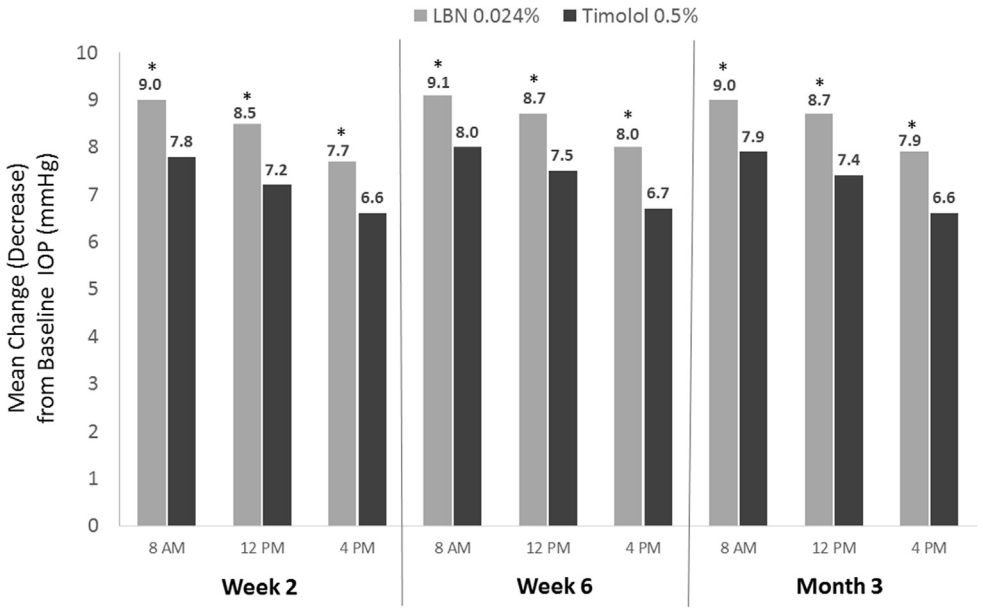

Figure 3. Change from baseline in mean intraocular pressure (IOP) (mmHg) in the study eye by visit, time point, and treatment group (intent-to-treat [ITT] population with with last observation carried forward [LOCF]). Mean was the least squares mean of the mean IOP change. LBN = latanoprostene bunod. *$P \leq$ 0.002 versus timolol at the same assessment point.

Table 4. Ocular Treatment-Emergent Adverse Events Occurring in ≥1% of Study and Treated Fellow Eyes in Either Treatment Group (Safety Population)

	LBN 0.024%		Timolol 0.5%	
	Study Eye N = 283	*Fellow Treated Eye N = 276*	*Study Eye N = 135*	*Fellow Treated Eye N = 134*
	n (%)	*n (%)*	*n (%)*	*n (%)*
≥1 ocular TEAE	38 (13.4)	40 (14.5)	16 (11.9)	17 (12.7)
≥1 treatment-related ocular TEAE	31 (11.0)	31 (11.2)	12 (8.9)	12 (9.0)
Eye irritation	11 (3.9)	10 (3.6)	3 (2.2)	3 (2.2)
Conjunctival hyperemia	8 (2.8)	10 (3.6)	2 (1.5)	3 (2.2)
Eye pain	4 (1.4)	7 (2.5)	3 (2.2)	1 (0.7)
Dry eye	3 (1.1)	2 (0.7)	1 (0.7)	1 (0.7)
Foreign body sensation in eyes	3 (1.1)	5 (1.8)	0 (0.0)	0 (0.0)
Instillation site pain	3 (1.1)	2 (0.7)	2 (1.5)	3 (2.2)

LBN = latanoprostene bunod; TEAE = treatment-emergent adverse event.

of a review of data from the UK Glaucoma Treatment Study evaluating the effect of latanoprost 0.005% compared with vehicle in patients with OAG.[11,29]

Results of secondary efficacy end points were consistent with the primary outcome measures. Significantly more subjects treated with LBN 0.024% than timolol 0.5% achieved predetermined criterions of an absolute IOP ≤18 mmHg or IOP reduction ≥25% at each of the 9 measured time points, and the CFB in mean IOP and mean diurnal IOP were consistently significantly greater in the LBN group throughout the study. Several landmark trials support the clinical practice of setting a target diurnal IOP in the treatment of patients with OAG or OHT and have demonstrated that IOP reduction to such targets slows the rate of development or progression of visual loss and structural damage caused by glaucoma.[5–7,9] The Advanced Glaucoma Intervention Study demonstrated that patients with glaucoma reaching and maintaining a target IOP of ≤18 mmHg through surgical intervention supplemented with medical treatment had a significantly reduced progression of visual field loss compared with eyes that failed to meet this target.[7] Likewise, in the Ocular Hypertension Treatment Study, in which treatment with IOP-lowering medication resulted in a 23% reduction in IOP, only 36 of 817 patients developed glaucoma by 60 months versus 89 of 819 patients in the observation group.[5] The Early Manifest Glaucoma Trial, in which treated patients had an average IOP lowering of 25%, demonstrated that IOP-lowering treatment halved the risk of disease progression in patients with OAG (hazard ratio, 0.50; 95% CI, 0.35–0.71).[6,9]

Intraocular pressure is the only modifiable risk factor in patients with OAG, with numerous studies demonstrating a relationship between IOP lowering and slowed progression or prevention of OAG, regardless of the interventional method.[5–11,30–34] Treatment options include pharmacotherapy, laser therapy, and surgery, and the choice of therapy should be individualized in consideration of patient factors and preferences. Pharmacologic treatment with prostaglandin analogs or β-blockers commonly is used as initial intervention for IOP lowering in patients with OAG.[35] Features such as IOP-lowering potential, safety, and dosing convenience are important considerations.

Latanoprostene bunod is a novel monotherapy with the pharmacologic activity of both a prostaglandin F2α analog (latanoprost acid) and, via the NO donating moiety, the physiologic signaling mediator NO. Both active moieties of LBN independently have been shown to lower IOP via 2 distinct mechanisms: latanoprost acid via the uveoscleral (nonconventional) aqueous outflow pathway and NO via the trabecular meshwork/Schlemm's canal (conventional) outflow pathway.[15–27] The intent in the development of this new monotherapy was to provide enhanced IOP-lowering potential over currently available glaucoma therapies without an increased risk of adverse events.

The additional IOP lowering by LBN over latanoprost 0.005% (Xalatan, Pfizer, New York, NY) has been demonstrated in both nonclinical animal models of OHT and a phase 2 clinical study.[13,14] The phase 2 study compared LBN with latanoprost in 396 patients with OAG and OHT (the VOYAGER study).[14] After 28 days of once-daily treatment in the evening, the reduction in mean diurnal IOP from baseline was significantly greater with LBN 0.024% than with latanoprost 0.005% (−9.0 vs. −7.8 mmHg, $P = 0.005$). These findings are suggestive of an additive benefit of the NO-donating component of LBN. Although the current study did not include a latanoprost comparator arm, an additional IOP lowering of >1 mmHg over timolol was apparent at all evaluation time points over 3 months.

In addition to IOP-lowering effectiveness, it is important that LBN not be associated with clinically limiting safety or tolerability issues. In the current study, the adverse event profiles of LBN and timolol were similar over the 3 months of treatment. In fact, TEAEs were fairly uncommon in both groups, and reports of eye pain and irritation were low. Visual acuity findings and vital signs measurements were unremarkable. Although the overall proportions of subjects with ocular hyperemia as assessed by investigators were similar between treatment groups both before and after treatment at each visit, a greater proportion of subjects in the LBN group were rated as having moderate to severe hyperemia compared with subjects in the timolol group. These findings are consistent with reported rates of hyperemia in patients treated with latanoprost.[36]

In conclusion, LBN 0.024%, a once-daily NO-donating prostaglandin monotherapy with a dual mechanism of action, was safe and significantly more effective than timolol 0.5% BID in reducing mean IOP in patients with OAG and OHT. The ability to more consistently lower IOP to ≤18 mmHg may provide a significant advantage over topical β-blockers.

Acknowledgments. Editorial assistance was provided by Churchill Communications (Maplewood, NJ) and funded by Bausch & Lomb, Inc.

References

1. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet 2004;363:1711–20.
2. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA 2014;311:1901–11.
3. Varma R, Lee PP, Goldberg I, Kotak S. An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol 2011;152:515–22.
4. Armaly MF, Krueger DE, Maunder L, et al. Biostatistical analysis of the collaborative glaucoma study, I: summary report of the risk factors for glaucomatous visual-field defects. Arch Ophthalmol 1980;98:2163–71.
5. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: a randomized trial determines that topical hypotensive medication delays or prevents the onset of primary open angle glaucoma. Arch Ophthalmol 2002;120:701–3.
6. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002;120:1268–79.
7. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000;130:429–40.
8. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001;108:1943–53.
9. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol 2003;121:48–56.
10. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;126:487–97.
11. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomized, multicentre, placebo-controlled trial. Lancet 2015;385:1295–304.
12. Schmier JK, Hulme-Lowe CK, Covert DW. Adjunctive therapy patterns in glaucoma patients using prostaglandin analogs. Clin Ophthalmol 2014;8:1097–104.
13. Krauss AH, Impagnatiello F, Toris CB, et al. Ocular hypotensive activity of BOL-303259-X, a nitric oxide donating prostaglandin F2α agonist, in preclinical models. Exp Eye Res 2011;93:250–5.
14. Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. Br J Ophthalmol 2015;99:738–45.
15. Lindsey JD, Kashiwagi K, Kashiwagi F, Weinreb RN. Prostaglandins alter extracellular matrix adjacent to human ciliary muscle cells in vitro. Invest Ophthalmol Vis Sci 1997;38:2214–23.
16. Schachtschabel U, Lindsey JD, Weinreb RN. The mechanism of action of prostaglandins in uveoscleral outflow. Curr Opin Ophthalmol 2000;11:112–5.
17. Gaton DD, Sagara T, Lindsey JD, et al. Increased matrix metalloproteinases 1, 2, and 3 in the monkey uveoscleral outflow pathway after topical prostaglandin F(2 alpha)-isopropyl ester treatment. Arch Ophthalmol 2001;119:1165–70.
18. Richter M, Krauss AH, Woodward DF, Lutjen-Drecoll E. Morphological changes in the anterior eye segment after long-term treatment with different receptor selective prostaglandin agonists and a prostamide. Invest Ophthalmol Vis Sci 2003;44:4419–26.
19. Nathanson JA. Nitrovasodilators as a new class of ocular hypotensive agents. J Pharmacol Exp Ther 1992;260:956–65.
20. Schuman JS, Erickson K, Nathanson JA. Nitrovasodilator effects on intraocular pressure and outflow facility in monkeys. Exp Eye Res 1994;58:99–105.
21. Wiederholt M, Sturm A, Lepple-Wienhues A. Relaxation of trabecular meshwork and ciliary muscle by release of nitric oxide. Invest Ophthalmol Vis Sci 1994;35:2515–20.
22. Schneemann A, Dijkstra BG, van den Berg TJ, et al. Nitric oxide/guanylate cyclase pathways and flow in anterior segment perfusion. Graefes Arch Clin Exp Ophthalmol 2002;240:936–41.
23. Kotikoski H, Vapaatalo H, Oksala O. Nitric oxide and cyclic GMP enhance aqueous humor outflow facility in rabbits. Curr Eye Res 2003;26:119–23.
24. Heyne GW, Kiland JA, Kaufman PL, Gabelt BT. Effect of nitric oxide on anterior segment physiology in monkeys. Invest Ophthalmol Vis Sci 2013;54:5103–10.
25. Cavet ME, Vittitow JL, Impagnatiello F, et al. Nitric oxide (NO): an emerging target for the treatment of glaucoma. Invest Ophthalmol Vis Sci 2014;55:5005–15.
26. Chang JY, Stamer WD, Bertrand J, et al. Role of nitric oxide in murine conventional outflow physiology. Am J Physiol Cell Physiol 2015;309:C205–14.
27. Lei Y, Zhang X, Song M, et al. Aqueous humor outflow physiology in NOS3 knockout mice. Invest Ophthalmol Vis Sci 2015;56:4891–8.
28. Higginbotham EJ, Olander KW, Kim EE, et al. Fixed combination of latanoprost and timolol vs individual components for primary open-angle glaucoma or ocular hypertension: a randomized, double-masked study. Arch Ophthalmol 2010;128:165–72.
29. Heijl A. Glaucoma treatment: by the highest level of evidence. Lancet 2015;385:1264–6.
30. Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Follow-up Study: 7. Results. Am J Ophthalmol 1995;120:718–31.
31. Migdal C, Gregory W, Hitchings R. Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma. Ophthalmology 1994;101:1651–6.
32. Mao LK, Stewart WC, Shields MB. Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma. Am J Ophthalmol 1991;111:51–5.

33. Kidd MN, O'Connor M. Progression of field loss after trabeculectomy: a five-year follow-up. Br J Ophthalmol 1985;69:827–31.
34. Chauhan BC, Mikelberg FD, Balaszi G, et al. Canadian Glaucoma Study: 2. Risk Factors for the Progression of Open-Angle Glaucoma. Arch Ophthalmol 2008;126:1030–6.
35. American Academy of Ophthalmology. Preferred Practice Pattern. Primary open-angle glaucoma 2010;. Available at: http://www.aao.org/preferred-practice-pattern/primary-openangle-glaucoma-ppp—october-2010. Accessed June 25, 2015.
36. Zhang WY, Po AL, Dua HS, Azuara-Blanco A. Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. Br J Ophthalmol 2001;85:983–90.

Footnotes and Financial Disclosures

Originally received: November 20, 2015.
Final revision: January 4, 2016.
Accepted: January 13, 2016.
Available online: February 11, 2016. Manuscript no. 2015-2057.

[1] Hamilton Glaucoma Center, Shiley Eye Institute and Department of Ophthalmology, University of California San Diego, La Jolla, California.

[2] Bausch & Lomb, Bridgewater, New Jersey.

[3] Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University Medical Center, New York, New York.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): R.N.W.: Personal fees – Bausch & Lomb, during the conduct of the study; Personal fees – Allergan and Alcon; Personal fees and nonfinancial support – Carl Zeiss; Grants – Genentech; nonfinancial support – Optovue; Personal fees and nonfinancial support – Topcon, outside the submitted work.

B.S.S.: Personal fees – Bausch & Lomb, during the conduct of the study, and personal fees – Allergan, outside the submitted work.

J.V.: Personal fees – Bausch & Lomb, during the conduct of the study.

J.L.: Personal fees – Alcon, Allergan, and Bausch & Lomb, during the conduct of the study.

Author Contributions:

Conception and design: Weinreb, Sforzolini, Vittitow

Data collection: Weinreb, Vittitow, Liebmann

Analysis and interpretation: Weinreb, Sforzolini, Vittitow, Liebmann

Obtained funding: Not applicable

Overall responsibility: Weinreb, Sforzolini, Vittitow, Liebmann

Abbreviations and Acronyms:
ANCOVA = analysis of covariance; **BCVA** = best-corrected visual acuity; **BID** = twice daily; **CFB** = change from baseline; **CI** = confidence interval; **IOP** = intraocular pressure; **ITT** = intent-to-treat; **LBN** = latanoprostene bunod; **LOCF** = last observation carried forward; **logMAR** = logarithm of the minimum angle of resolution; **NO** = nitric oxide; **OAG** = open-angle glaucoma; **OHT** = ocular hypertension; **PP** = per-protocol; **qPM** = every evening; **SD** = standard deviation; **TEAE** = treatment-emergent adverse event; **WOCF** = worst observation carried forward.

Correspondence:
Robert N. Weinreb, MD, University of California, San Diego, 9500 Gilman Dr., MC 0946, La Jolla, CA 92093. E-mail: Rweinreb@ucsd.edu.