Comparison of Latanoprostene Bunod 0.024% and Timolol Maleate 0.5% in Open-Angle Glaucoma or Ocular Hypertension: The LUNAR Study

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• PURPOSE: To compare the intraocular pressure (IOP)-lowering effect of latanoprostene bunod (LBN) 0.024% with timolol maleate 0.5% in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT).

• DESIGN: Prospective, randomized, double-masked, parallel-group, noninferiority clinical trial.

• METHODS: Adults with OAG or OHT from 46 clinical sites (United States and European Union) were randomized 2:1 to LBN instilled once daily (QD) in the evening and vehicle in the morning or timolol instilled twice a day (BID) for 3 months. IOP was measured at week 2, week 6, and month 3 (8 AM, 12 PM, and 4 PM each visit).

• RESULTS: A total of 387 subjects (LBN, n = 259; timolol, n = 128) completed the study. Analysis of covariance showed that mean IOP reduction with LBN was not only noninferior to timolol but significantly greater ($P \leq .025$) than timolol at all but the first time point in this study (week 2, 8 AM). Of LBN- and timolol-treated subjects, respectively, 31.0% and 18.5% ($P = .007$) had their IOP reduced ≥25% from baseline, and 17.7% and 11.1% ($P = .084$) had their IOP reduced to ≤18 mm Hg over all time points/visits in this study. Ocular treatment-emergent adverse events, while uncommon, appeared more frequently in the LBN group (all mild-moderate except 1 case of severe hyperemia).

• CONCLUSIONS: LBN 0.024% QD in the evening was noninferior to timolol 0.5% BID over 3 months of treatment, with significantly greater IOP lowering in subjects with OAG or OHT at all but the earliest time point evaluated, and demonstrated a good safety profile. (Am J Ophthalmol 2016;168:250–259.

LATANOPROSTENE BUNOD (LBN; BOL-303259-X; Bausch + Lomb) is a novel nitric oxide–donating prostaglandin F2α analogue. The compound is rapidly metabolized into latanoprost acid, a prostaglandin analogue, and butanediol mononitrate, a nitric oxide (NO)-donating moiety, following exposure to esterases in the ocular environment.[1] Prostaglandin analogues and NO donors have both demonstrated intraocular pressure (IOP)-lowering effects in animals and humans.[2–13] Latanoprost (Xalatan; Pfizer Inc, New York, New York, USA), which is hydrolyzed in the cornea to latanoprost acid, is indicated for the reduction of elevated IOP in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT).[14] Data indicate that the effects of LBN on IOP are mediated via actions on both nonconventional and conventional aqueous outflow pathways. Whereas latanoprost reduces IOP by increasing the outflow of aqueous fluid primarily through the uveoscleral pathway (nonconventional route),[15–22] NO donors are reported to induce relaxation of the trabecular meshwork and the Schlemm's canal, which increases aqueous humor outflow through the conventional pathway.[2,4,5,12,13,23–28]

In 3 preclinical models of ocular hypertension (laser-induced ocular hypertensive nonhuman primate, glaucomatous dog, and transiently ocular hypertensive rabbit), topical administration of LBN rapidly lowered IOP.[1] The rabbit model was insensitive to equimolar latanoprost, suggesting that the effects of LBN in this model were solely mediated by NO. Further, the IOP-lowering effects of LBN were greater than those of equimolar doses of latanoprost in both glaucomatous dogs and ocular hypertensive primates, presumably owing to the action of NO. In a randomized, investigator-masked, parallel-group, dose-ranging, phase 2 clinical study in 413 patients with OAG or OHT, LBN ophthalmic solution 0.024% reduced mean diurnal IOP to a significantly greater extent than latanoprost 0.005% (Xalatan) over 28 days of treatment.[29] This improvement

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in IOP reduction with LBN 0.024% relative to latanoprost 0.005% in human subjects with OAG or OHT confirmed preclinical findings, providing additional support for a pharmacologic effect of NO released from the NO-donating portion of the LBN molecule.

The objective of this phase 3 study was to compare the IOP-lowering effect of LBN 0.024% instilled once daily (QD) in the evening with timolol maleate 0.5% (hereafter referred to as timolol 0.5%) instilled twice daily (BID) in subjects with OAG or OHT. Another recent phase 3 trial with a similar design (the APOLLO study)[30] found that LBN QD in the evening was significantly better than timolol 0.5% BID with regard to IOP lowering throughout the day.

METHODS

• **STUDY DESIGN:** The LUNAR study (Clinicaltrials.gov identifier: NCT01749930) was a randomized, multicenter, double-masked, parallel-group, clinical study conducted at 46 investigational sites in the United States (40), the United Kingdom (3), Germany (2), and Italy (1) between January 28, 2013 and November 26, 2014. The study was conducted in accordance with Good Clinical Practices (as described in the International Conference on Harmonization guidelines), the ethical principles of the Declaration of Helsinki, the Code of Federal Regulations, and applicable local regulations. Institutional Review Board/Ethics Committee approval was obtained at each participating site, and all study subjects provided written informed consent prior to participation. The primary objective of the study was to evaluate the noninferiority of the mean IOP-lowering effect of LBN 0.024% over 3 months of treatment to that of timolol 0.5%. If noninferiority of LBN 0.024% was achieved, the secondary objective was to evaluate the statistical superiority of LBN 0.024% to timolol 0.5%. The study was composed of 2 phases: a 3-month active controlled efficacy phase followed by a 3-month open-label safety extension phase, the results of which will be published separately.

• **SUBJECTS:** The study enrolled male and female subjects ≥18 years of age with a diagnosis of OAG (including pigmentary or pseudoexfoliative) or OHT in 1 or both eyes. Intraocular pressure was assessed once at visit 1 (Screening) and at 8 AM, 12 PM, and 4 PM during visit 3 (Eligibility, Day 0) to establish baseline and eligibility values. Subjects who were already receiving treatment with an IOP-lowering medication were required to undergo a washout period prior to visit 3, the duration of which varied depending on the type of IOP-lowering medication used (maximum washout period, 28 + 5 days). At visit 3, and following washout, if required, study participants were required to have an IOP ≥26 mm Hg at a minimum of 1 of 3 time points (8 AM, 12 PM, and 4 PM), ≥24 mm Hg at a minimum of 1 time point, and ≥22 mm Hg at 1 time point, all in the same eye, and IOP ≤36 mm Hg at all 3 measurement time points in both eyes. Potential subjects undergoing washout were excluded from participation in the study if IOP exceeded 36 mm Hg in either eye at any point during the washout period. Eligible subjects also had a best-corrected visual acuity (BCVA) of + 0.7 logarithm of the minimal angle of resolution (logMAR) units (Snellen equivalent of approximately 20/100) or better in either eye.

Subjects were ineligible for study participation if they were involved in another clinical trial during this study, or were involved in another clinical trial within 30 days prior to visit 1 (Screening), for subjects requiring a washout period, or 30 days prior to visit 3 (Eligibility, Day 0) for subjects not requiring a washout period. Subjects were also excluded if they had known hypersensitivity or contraindication to the active or inactive ingredients of the study treatments; were unable to discontinue contact lens use or other eye drop medications (eg, artificial tears) during and for 15 minutes after instillation of study drug and during study visits; had a central corneal thickness >600 μm in either eye; had any condition that prevented reliable applanation tonometry (eg, significant corneal surface abnormalities) in either eye; or had advanced glaucoma (cup-to-disc ratio >0.8 or split fixation) or other significant ophthalmic disease. The study also excluded subjects who required treatment with ocular or systemic corticosteroids, subjects in need of or expected to require additional topical or systemic treatment for OAG or OHT, and subjects with an anticipated need to initiate or modify medication known to affect IOP (eg, β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme A inhibitors and angiotensin II receptor blockers) during the study.

• **STUDY TREATMENTS AND ASSESSMENTS:** The investigational product LBN 0.024%, its vehicle, and the comparator timolol 0.5% were manufactured by Bausch & Lomb Inc (Tampa, Florida, USA). Baseline demographic and clinical data (ie, relevant medical and ocular history, concomitant medications, ocular assessments) were recorded at visit 1 (Screening). The study eye was defined as the eye that qualified per inclusion criteria at visit 3 (Eligibility, Day 0). If both eyes qualified, the study eye was the eye with the higher mean diurnal IOP value (defined as average of IOPs recorded at 8 AM, 12 PM, and 4 PM) at visit 3, 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 met study inclusion criteria at visit 3.

Eligible subjects were randomized at visit 3 in a 2:1 ratio to receive 3 months of treatment with LBN 0.024% QD in the evening (approximately 8 PM) and vehicle QD in the morning (approximately 8 AM) or timolol 0.5% BID.

Each subject received study kits containing 4 eye drop bottles with computer-generated investigational labels (ie, void of commercial labeling) and was instructed to instill 1 drop of study drug from the "Night" dosing bottle into the affected eye(s) at approximately 8 PM each evening and 1 drop from the "Day" dosing bottle at approximately 8 AM each morning. A randomization schedule was created prior to any study enrollment by a statistician not otherwise involved in the study using SAS (SAS Institute, Cary, North Carolina, USA; Version 9.2). Allocation of study drug was completed through the use of IRT (Interactive Response Technology), which determined which kit to assign to each subject. Subjects and study site personnel were fully masked to treatment assignments. Compliance was determined as actual number of instillations, as recorded on a patient diary, divided by number of expected instillations.

Subjects completed 3 study visits (visit 4 [week 2 ± 2 days]; visit 5 [week 6 ± 3 days]; visit 6 [month 3 ± 10 days]) following randomization. Intraocular pressure was assessed at each visit in both eyes at 8 AM, 12 PM, and 4 PM using a Goldman applanation tonometer. On these days, the AM dose of study drug was instilled after the first IOP assessment of the day. Intraocular pressure was measured twice consecutively and the mean IOP was recorded for consecutive measurements within 2 mm Hg. In cases of consecutive measurements differing by >2 mm Hg, a third measurement was taken and the median IOP was recorded. Whenever possible, IOP was measured by the same operator using the same tonometer at each visit for a given subject.

Safety assessments recorded at each visit included ocular and systemic treatment-emergent adverse events (TEAEs), vital sign measurements, BCVA (measured using the ETDRS standard protocol), and slit-lamp examination; in addition, ophthalmoscopy and specular microscopy were performed at day 0 and month 3. Conjunctival hyperemia was graded by the investigator on a 1-4 photographic reference (none, mild, moderate, severe) scale prior to IOP assessment at each time point/study visit.

• **ENDPOINTS:** The primary efficacy endpoint was the IOP in the study eye measured at the specified time points of 8 AM, 12 PM, and 4 PM at each postrandomization visit (week 2, week 6, and month 3). Secondary efficacy endpoints included the proportion of eyes with IOP ≤18 mm Hg; the proportion with IOP reduction ≥25% from baseline consistently across all 9 postrandomization assessments; change from baseline in IOP at 8 AM, 12 PM, and 4 PM; and the change from baseline in diurnal IOP at week 2, week 6, and month 3. Safety endpoints included the incidence of ocular and systemic adverse events (AEs), vital signs, BCVA, and conjunctival hyperemia assessments.

• **STATISTICAL ANALYSIS:** A sample size of 300 subjects in the per-protocol (PP) population was calculated as providing adequate power (90%) to detect an IOP difference (noninferiority margin) of 1.5 mm Hg, assuming a standard deviation (SD) of 3.75 mm Hg and a 2-sided $\alpha = 0.05$. The SD was obtained by pooling the SD from an LBN 0.024% phase 2b study[29] and the timolol arm of a phase 3 study.[31] A total of 393 subjects were to be randomized in a 2:1 ratio to the LBN 0.024% and timolol 0.5% treatment groups, respectively, to account for potential protocol violations and dropouts.

The primary efficacy analyses were performed using analysis of covariance (ANCOVA) in the intent-to-treat (ITT) population (ie, all randomized subjects who instilled at least 1 dose of study drug and had a baseline and at least 1 postrandomization IOP), with randomized treatment group as a classification variable and time-matched mean IOP as a covariate. Missing data were imputed using the last-observation-carried-forward (LOCF) method for the IOP in the study eye measured at 8 AM, 12 PM, and 4 PM at each postrandomization visit. The 2 treatments, LBN 0.024% and timolol 0.5%, were compared for each time point at each visit by determining the least squares (LS) mean of each treatment group, the difference in the LS mean (LBN 0.024% – timolol 0.5%), and the 2-sided 95% confidence interval (CI) for the difference. Noninferiority was to be established if the upper limit of the CIs for the difference did not exceed 1.5 mm Hg at all 9 IOP assessments and did not exceed 1.0 mm Hg for at least 5 out of the 9 time points. If noninferiority was determined, superiority was concluded if the upper limit of the 95% CI did not exceed 0 mm Hg at any of the 9 IOP measurement time points. These analyses were repeated in the PP population in order to supplement the primary analyses.

Analyses of the secondary endpoints were performed following demonstration of noninferiority of LBN 0.024% to timolol 0.5%. The proportion of subjects with IOP ≤18 mm Hg at all 9 postrandomization IOP measurement time points and the proportion with IOP reduction ≥25% at all 9 time points were summarized categorically. The percentage reduction from baseline in IOP was calculated as 100 × (baseline mean IOP − postbaseline mean IOP)/baseline mean IOP. For each secondary endpoint, the 2-sided 95% CI around the difference in proportions (LBN 0.024% − timolol 0.5%) and the *P* value from the Pearson χ^2 test were presented. An ANCOVA of change from baseline in IOP was performed with fixed-effect terms for treatment and baseline for the 3 postrandomization time points (8 AM, 12 PM, and 4 PM) at visit 4/week 2, visit 5/week 6, and visit 6/month 3. An ANCOVA of change from baseline in mean diurnal IOP was also performed with fixed-effect terms for treatment and diurnal baseline IOP at each postrandomization visit.

Safety analyses were performed on the safety population, which included all randomized subjects who instilled at least 1 dose of study drug. All AEs were coded using Medical Dictionary for Regulatory Activities dictionary version 13.0. Ocular TEAEs were summarized for study eyes and treated fellow eyes separately by treatment group. Nonocular TEAEs were summarized for each treatment group using

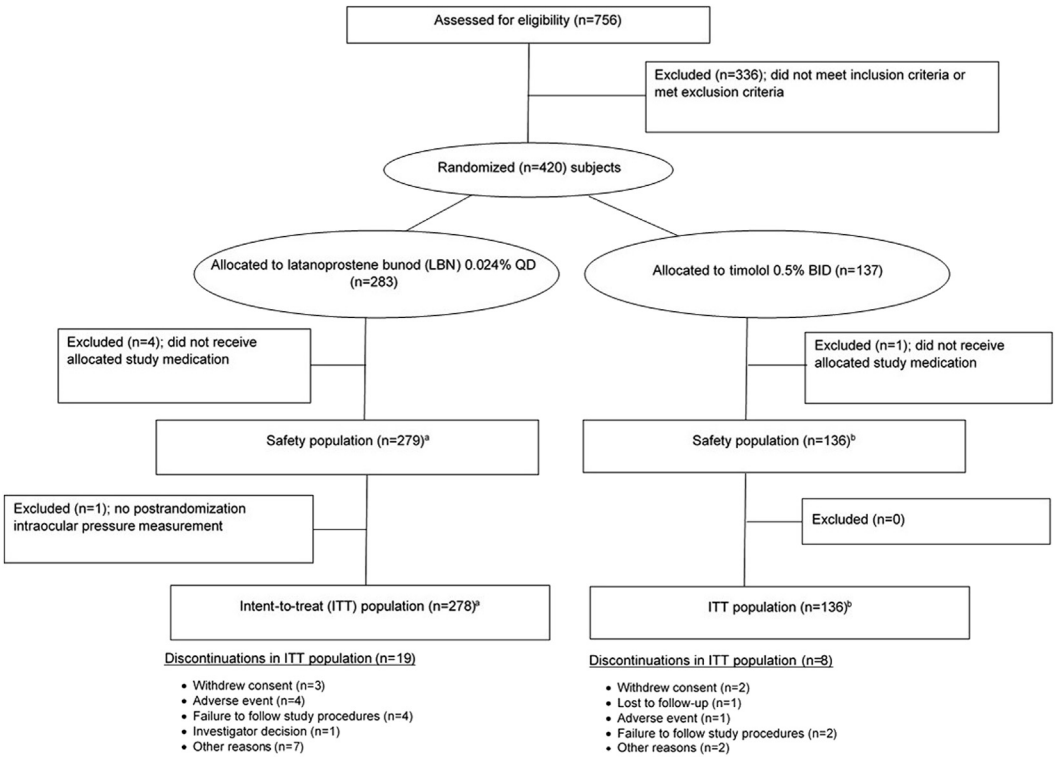

FIGURE 1. Disposition of patients with open-angle glaucoma or ocular hypertension receiving latanoprostene bunod 0.024% or timolol 0.5%. [a]In 2 latanoprostene bunod (LBN) subjects, including the subject excluded from the intent-to-treat (ITT) population, the study eye could not be derived according to the protocol definition. Thus, the number of evaluable study eyes was n = 277 for both the safety and ITT populations. [b]In 1 timolol subject, the study eye could not be derived according to the protocol definition. Thus, the number of evaluable study eyes was n = 135 for both the safety and ITT populations.

discrete summaries at the subject and event level by system organ class and preferred term. Ocular and nonocular TEAEs were summarized by relationship to study drug and severity. Data on BCVA, conjunctival hyperemia, slit-lamp biomicroscopy, and ophthalmoscopy were presented separately for study eyes and treated fellow eyes and summarized using descriptive statistics (BCVA) or categorically (conjunctival hyperemia, slit-lamp biomicroscopy, and ophthalmoscopy). Conjunctival hyperemia was classified as none, mild, moderate, or severe through the use of photographic standards.

All CIs, statistical tests, and resulting *P* values were reported as 2-sided and were evaluated at the 5% significance level. Continuous data were summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum). Statistical analyses were conducted using SAS software (SAS Institute, Cary, North Carolina, USA) version 9.2 or higher.

RESULTS

• **SUBJECTS:** Of 756 subjects screened, 420 were enrolled and randomized to LBN 0.024% (n = 283) or timolol 0.5% (n = 137), and 387 (92.1%) completed the 3 months of study treatment (Figure 1). Overall, 415 subjects received at least 1 instillation of study drug and comprised the safety population. The ITT population included 414 subjects (LBN 0.024%, n = 278; timolol 0.5%, n = 136). The proportion of subjects in the ITT population who completed the study was similar in the LBN 0.024% (259/278; 93.2%) and timolol 0.5% (128/136; 94.1%) groups.

In the ITT population, subjects were on average 64.7 years of age (range, 23–88 years) and were predominantly female (58.2%), white (70.8%), and non-Hispanic/non-Latino (86.7%; Table 1). Black/African-American subjects comprised 27.8% of the overall population. Demographic and baseline eye characteristics (mean corneal thickness, refraction sphere, and refraction cylinder) were comparable between treatment groups. The majority of subjects (72%) had been treated with IOP-lowering medications within 30 days prior to enrollment. Nonocular medical history was similar between the treatment groups. Baseline mean (SD) diurnal IOP (average of IOP at 8 AM, 12 PM, and 4 PM) was 26.6 (2.4) mm Hg for subjects randomized to LBN 0.024% and 26.4 (2.3) mm Hg for subjects randomized to timolol 0.5%.

TABLE 1. Demographics and Baseline Ocular Characteristics of Subjects Randomized to Latanoprostene Bunod 0.024%, Timolol 0.5% and Overall (Intent-to-Treat Population)

	Latanoprostene Bunod 0.024% (n = 278)	Timolol 0.5% (n = 136)	Total (N = 414)
Demographics			
Age, y			
Mean (SD)	65.0 (9.77)	64.1 (9.71)	64.7 (9.75)
Median (range)	66.0 (23–87)	65.0 (37–88)	65.0 (23–88)
Age group, n (%)			
<65 years	127 (45.7)	64 (47.1)	191 (46.1)
≥65 years	151 (54.3)	72 (52.9)	223 (53.9)
Sex, n (%)			
Male	116 (41.7)	57 (41.9)	173 (41.8)
Female	162 (58.3)	79 (58.1)	241 (58.2)
Race, n (%)			
White	204 (73.4)	89 (65.4)	293 (70.8)
Black or African-American	69 (24.8)	46 (33.8)	115 (27.8)
Asian	4 (1.4)	1 (0.7)	5 (1.2)
Other	1 (0.4)	0	1 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	36 (12.9)	19 (14.0)	55 (13.3)
Non-Hispanic and non-Latino	242 (87.1)	117 (86.0)	359 (86.7)
On IOP-lowering medication at enrollment, n (%)[a]			
Yes	196 (70.5)	102 (75.0)	298 (72.0)
No	82 (29.5)	34 (25.0)	116 (28.0)
Baseline Ocular Characteristics[b]			
Mean corneal thickness, μm			
Mean (SD)	550.17 (31.11)	551.18 (32.67)	550.50 (31.59)
Median	551.33	556.33	553.66
Min, max	470, 598.66	436, 598.66	436, 589.66
Diurnal intraocular pressure, mm Hg, mean (SD)	26.6 (2.39)	26.4 (2.30)	26.5 (2.36)

IOP = intraocular pressure; SD = standard deviation.

[a]Previous IOP-lowering medication categories: prostaglandin analogues (80.9%), β-blockers/combination drugs with a β-blocker (24.2%), sympathomimetics (7.4%), and miotics or carbonic anhydrase inhibitors (14.1%).

[b]Study eye could not be derived for 2 subjects; latanoprostene bunod n = 277; timolol n = 135 for baseline ocular characteristics.

• **EFFICACY:** *Primary endpoint*. The mean IOP in the study eye was significantly lower in the LBN 0.024% group than in the timolol 0.5% group at the majority of time points measured (12 PM, 4 PM at week 2, 8 AM, 12 PM, 4 PM at week 6 and month 3) (Figure 2 and Table 2). Noninferiority of LBN 0.024% to timolol 0.5% was demonstrated based on ANCOVA results (upper limit of the 95% CIs did not exceed 1.0 mm Hg at any of the 9 time points) (Table 2). LBN 0.024% also met the criteria for statistical superiority over timolol 0.5% at all time points except the 8 AM time point at week 2 (upper limit of the 95% CI exceeded 0 mm Hg at this single assessment point) (Table 2). Results in the PP population were consistent with these findings (data not shown). Further exploratory analysis indicated that the primary endpoint results did not differ based on prior IOP-lowering medication treatment status at enrollment or whether or not subjects on concurrent systemic β-blockers (15.1% of LBN and 13.2% of timolol subjects) were included in the analysis (data not shown).

Secondary endpoints. The percentage of subjects with an IOP reduction ≥25% consistently at all 9 time points was significantly higher in the LBN group (31.0%) compared with the timolol group (18.5%; difference of proportions 12.5%; 95% CI of the difference: 4.0%, 21.1%; $P = .007$) (Figure 3). The percentage of subjects with mean IOP ≤18 mm Hg consistently at all 9 time points did not differ in the LBN group compared with the timolol group (17.7% vs 11.1%, respectively; difference of proportions, 6.6%; 95% CI: −0.4%, 13.5%; $P = .084$) (Figure 3).

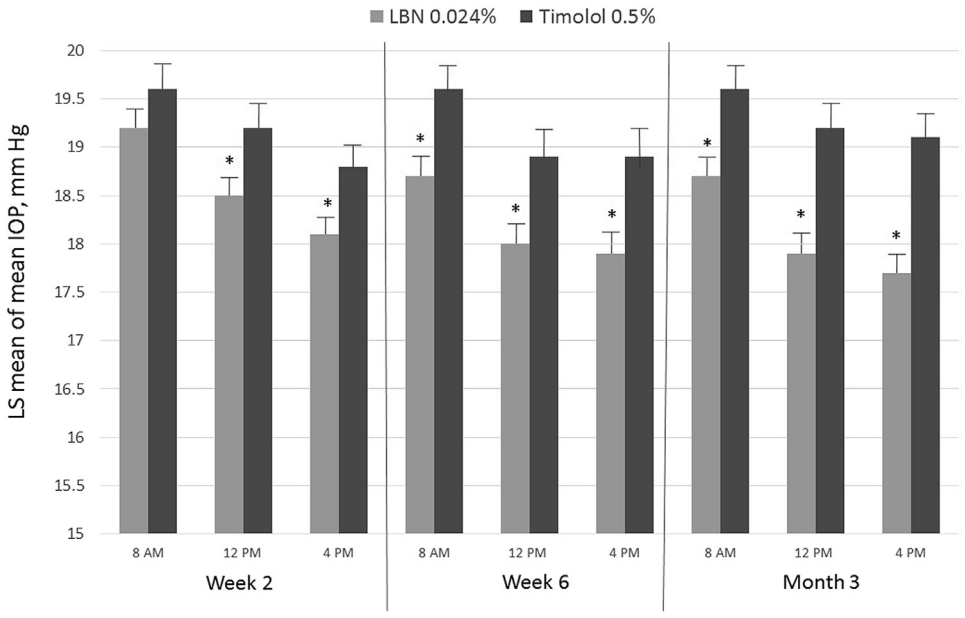

FIGURE 2. Least squares (LS) mean of mean intraocular pressure (IOP) (mm Hg) and standard error in the study eye by visit, time point, and treatment group among subjects treated with latanoprostene bunod 0.024% (LBN) once daily (n = 278) or timolol maleate 0.5% twice daily (n = 136). Data represent intent-to-treat population with last observation carried forward. *$P \leq .025$, analysis of covariance of treatment difference.

Further, ANCOVA showed that the treatment difference for the change from baseline in IOP was significantly greater in the LBN 0.024% group than in the timolol 0.05% group at all time points (IOP range −7.5 to −8.8 mm Hg for LBN 0.024%; −6.6 to −7.9 mm Hg for timolol 0.5%; $P \leq .025$) except for the 8 AM measurement at week 2 (−8.3 mm Hg for LBN 0.024% vs −7.9 mm Hg for timolol 0.5%; $P = .216$). These changes corresponded to a reduction from baseline ranging from 29.1% to 32.1% in the LBN 0.024% group and ranging from 25.2% to 28.7% in the timolol treatment group (Supplemental Table; Supplemental Material available at AJO.com).

Mean diurnal IOP was significantly lower in the LBN 0.024% group compared with the timolol 0.5% group at each visit (18.6 mm Hg vs 19.2 mm Hg at week 2, 18.2 mm Hg vs 19.1 mm Hg at week 6, and 18.1 mm Hg vs 19.3 mm Hg at month 3; $P \leq .034$ for all). Similar to the change from baseline at individual time points, the mean change from baseline in mean diurnal IOP was significantly greater in the LBN 0.024% group than in the timolol 0.5% group at each postrandomization study visit (week 2, difference, −0.6 mm Hg; $P = .034$; week 6, difference, −0.9 mm Hg; $P = .002$; month 3, difference, −1.2 mm Hg; $P < .001$).

• **SAFETY:** In the safety population, the mean (SD) days of exposure to the study drug was 88.8 (17.6) days in the LBN 0.024% group and 91.4 (14.9) days in the timolol 0.5% group.

The percentage of subjects experiencing at least 1 ocular TEAE in the study eye appeared greater in the LBN 0.024% group than in the timolol 0.5% group (Table 3). The most frequently reported ocular TEAEs in LBN-treated study eyes were conjunctival hyperemia, eye irritation, and eye pain. Only 2 subjects in the LBN 0.024% group experienced ocular TEAEs in the study eye that were considered unrelated to the study drug; all other TEAEs were considered treatment-related. With the exception of 1 incident of severe conjunctival hyperemia in the LBN 0.024% group that was considered possibly related to the study drug, all ocular TEAEs in the study eye were mild or moderate in severity.

At least 1 ocular TEAE in the treated fellow eye was experienced by 24.8% of subjects in the LBN 0.024% group and 13.4% of those in the timolol 0.5% group. As with the study eye, the most commonly reported ocular TEAEs in the treated fellow eye were conjunctival hyperemia (9.3% LBN 0.024%, 0.7% timolol 0.5%), eye irritation (7.0% LBN 0.024%, 4.5% timolol 0.5%), and eye pain (6.7% LBN 0.024%, 3.0% timolol 0.5%). The percentage of subjects experiencing at least 1 treatment-related ocular TEAE in the treated fellow eye appeared greater in the LBN 0.024% group (23.3%) than in the timolol 0.5% group (12.7%). One subject in the LBN 0.024% group experienced severe conjunctival hyperemia that was possibly related to the study drug; all other ocular TEAEs in the treated fellow eye were mild or moderate in severity.

Nonocular TEAEs were reported for 36 of 278 (12.9%) LBN subjects and 18 of 136 (13.2%) timolol 0.5% subjects,

TABLE 2. Analysis of Covariance Results for Comparison of Mean Intraocular Pressure in the Study Eye by Visit and Time Point (Intent-to-Treat Population With Last Observation Carried Forward)

	Least Squares Mean of the Mean IOP, mm Hg			
	Latanoprostene Bunod 0.024%	Timolol 0.5%	Treatment Difference (95% Confidence Interval)	*P* Value
Week 2				
8 AM	19.2	19.6	−0.4 (−1.1, 0.3)	.216
12 PM	18.5	19.2	−0.8 (−1.4, −0.1)	.022
4 PM	18.1	18.8	−0.7 (−1.3, −0.1)	.025
Week 6				
8 AM	18.7	19.6	−0.9 (−1.6, −0.3)	.005
12 PM	18.0	18.9	−0.8 (−1.5, −0.2)	.007
4 PM	17.9	18.9	−1.0 (−1.6, −0.4)	.003
Month 3				
8 AM	18.7	19.6	−0.9 (−1.5, −0.3)	.006
12 PM	17.9	19.2	−1.3 (−1.9, −0.7)	<.001
4 PM	17.7	19.1	−1.3 (−2.0, −0.7)	<.001

ANCOVA = analysis of covariance; IOP = intraocular pressure.

Least squares mean of the mean IOP, 95% confidence intervals, and *P* values were from an ANCOVA model with treatment as a classification variable and time-matched baseline mean IOP as a covariate.

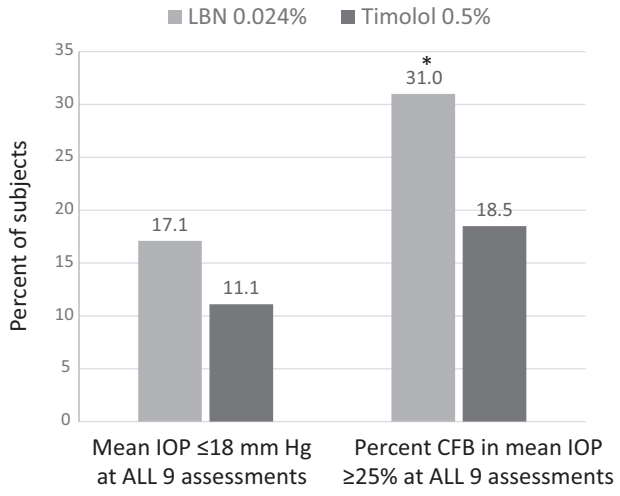

FIGURE 3. Percentage of subjects achieving a mean intraocular pressure (IOP) ≤18 mm Hg and percentage of subjects with a change from baseline (CFB) in IOP ≥25% at all 9 assessment time points in 387 subjects with open-angle glaucoma or ocular hypertension treated with latanoprostene bunod 0.024% once daily (n = 278) or timolol maleate 0.5% twice daily (n = 136). Data represent intent-to-treat population with last observation carried forward. *P = .007.

none of which were considered related to study treatment except for 6 events in 5 of 278 (1.8%) LBN subjects (madarosis, chest discomfort, dysgeusia, headache, insomnia, and dyspnea) and 4 events in 2 of 136 (1.5%) timolol subjects (headache [2 events], dizziness, somnolence). In the LBN group, 15 severe nonocular TEAEs were reported (coronary artery disease, cholelithiasis, fall in 2 subjects, head injury, joint dislocation in 2 subjects, scapular fracture, skin laceration, subdural hemorrhage, ulna fracture, arthralgia, convulsion, subarachnoid hemorrhage, and pulmonary embolism) and were considered unrelated or unlikely related to the study drug. One severe nonocular TEAE (headache) occurred in the timolol 0.5% group and was considered possibly related to the study drug. All other nonocular TEAEs were mild or moderate in severity.

Overall, 4 serious TEAEs were reported by 4 subjects (left shoulder subluxation/scapular fracture/fall, coronary artery disease, hepatobiliary disorders, and head injury in the LBN 0.024% group); none were considered related to the study drug. No deaths occurred during the 3-month efficacy phase.

There were 4 study discontinuations secondary to AEs in the LBN 0.024% group; 1 was deemed definitely related to the study drug (ocular hyperemia), while 3 were deemed probably related to the study drug (increased insomnia/respiratory disorder, blurred vision/instillation site pain, periocular rash). There was 1 AE-associated study discontinuation in the timolol 0.5% group (dizziness/headache), which was deemed possibly related to the study drug.

Vital sign measurements were similar between treatment groups with no treatment-related trends observed. LogMAR BCVA did not vary during the study. Study eye mean (SD) logMAR BCVA in LBN and timolol treatment groups was 0.09 (0.14) and 0.07 (0.12) at baseline and 0.08 (0.12) and 0.07 (0.13) at 3 months, respectively.

At baseline, 36.8% of subjects in the LBN group and 40.7% of subjects in the timolol group were found to have hyperemia in the study eye, mostly mild, as evaluated by the investigator. At each posttreatment visit, the percentage of subjects with investigator-assessed conjunctival

TABLE 3. Ocular Treatment-Emergent Adverse Events (TEAEs) Occurring in the Study Eye of ≥1% of Subjects in any Treatment Group (Safety Population)

	Latanoprostene Bunod 0.024%, n = 277[a] n (%)	Timolol Maleate 0.5%, n = 135[a] n (%)
≥1 ocular TEAE	66 (23.8)	18 (13.3)
≥1 treatment-related ocular TEAE	64 (23.1)	18 (13.3)
Eye disorders		
Conjunctival hyperemia	25 (9.0)	1 (0.7)
Eye irritation	20 (7.2)	6 (4.4)
Eye pain	16 (5.8)	5 (3.7)
Ocular hyperemia	7 (2.5)	1 (0.7)
Vision blurred	5 (1.8)	3 (2.2)
Eye pruritis	4 (1.4)	1 (0.7)
Asthenopia	0	2 (1.5)
Dry eye	3 (1.1)	1 (0.7)
Punctate keratitis	3 (1.1)	0
Foreign body sensation in eyes	3 (1.1)	0
Administration site conditions		
Instillation site pain	4 (1.4)	0
Investigations		
Corneal staining	3 (1.1)	0

[a]The study eye could not be derived for 3 subjects (2 in the latanoprostene bunod group, 1 in the timolol group) in the Safety population; there were no TEAEs reported for these subjects during the study.

hyperemia was slightly higher in the LBN treatment group compared with the timolol treatment group (week 2, 47.8% vs 36.6%; week 6, 47.8% vs 34.1%; month 3, 48.3% vs 31.5%), as was the percentage of subjects with conjunctival hyperemia considered moderate or severe (week 2, 6.2% vs 0.7%; week 6, 7.5% vs 3.0%; month 3, 6.5% vs 3.1%). Similar results were found for the treated fellow eye (data not shown).

DISCUSSION

THE FINDINGS FROM THIS RANDOMIZED, MULTICENTER, double-masked, parallel-group, clinical study demonstrate that LBN ophthalmic solution 0.024% QD in the evening effectively lowered IOP over 3 months of treatment in subjects with OAG or OHT. Noninferiority to timolol 0.5% BID was established by ANCOVA for the comparison of mean IOP. Treatment with LBN also resulted in significantly greater IOP lowering compared with timolol at all assessed time points except for the first postbaseline assessment at 8 AM/week 2 of treatment. As another measure of efficacy, IOP reduction responses were evaluated by the number of eyes demonstrating an IOP reduction that was ≥25% lower than the baseline value, and nearly twice as many subjects achieved this level of reduction across all 9 time points in the LBN group compared with the timolol group. Likewise, the percentage of subjects in whom IOP decreased to ≤18 mm Hg across all 9 time points was numerically higher in the LBN group compared with the timolol group, although the difference was not statistically significant.

Both LBN and timolol were well tolerated during the 3-month efficacy phase of this study. Although low overall, ocular AEs appeared more frequently in the LBN group and were mainly attributable to reports of conjunctival hyperemia and ocular irritation. Conjunctival hyperemia and ocular irritation were also the most commonly noted AEs reported with LBN use in another similarly designed 3-month, phase 3 comparison of LBN and timolol in 387 subjects with OAG or OHT.[30] Rates of hyperemia reported as an adverse event with LBN in the latter study[30] (2.8%–3.6%) were generally similar to those observed with timolol (1.5%–2.2%) and were lower than reported in the current study. According to investigator assessments, conjunctival hyperemia was present at baseline in about 40% of subjects in both the current and prior study[30] and showed slight variations in prevalence over 3 months of treatment, with LBN use associated with slightly higher rates compared with timolol. Conjunctival hyperemia is commonly encountered with the use of ocular antihypertensive therapy[32] including latanoprost,[33,34] and was therefore not unexpected whether reported as an AE or through prospective investigator evaluation. Other ocular AEs were infrequent and observed among similar proportions of patients in both study groups. Other safety outcomes were unremarkable.

Landmark studies such as the Ocular Hypertension Treatment Study (OHTS),[35] the Early Manifest Glaucoma Trial (EMGT),[36,37] the Canadian Glaucoma Study,[38] and the United Kingdom Glaucoma Treatment Study (UKGTS)[11] have demonstrated that in glaucoma suspects or patients with manifest glaucoma, the onset and/or progression of visual field loss and optic disc deterioration can be delayed by lowering IOP. Further, estimates based on some of these studies suggest that each 1 mm Hg reduction in IOP is associated with an approximate 10%–19% reduction in the risk for glaucoma progression.[37–39] In both the current study and the previously reported phase 3 trial with similar design,[30] there was an additional 1.2 mm Hg reduction in diurnal IOP with LBN as compared with timolol at 3 months. Further, IOP lowering observed with LBN 0.024% in these phase 3 studies[30] ranged from 7.5 to 9.1 mm Hg reductions from baseline over 3 months of treatment. The IOP reductions in the current study corresponded to percent decreases from baseline for LBN 0.024% ranging from 29% to 32%.

While phase 3 studies did not evaluate IOP lowering of LBN against the most commonly used glaucoma medication, latanoprost, a mixed treatment comparison meta-analysis of randomized controlled trials evaluating the IOP-lowering efficacy of prostaglandin analogues found an additional mean IOP lowering of 1.0 mm Hg for latanoprost over timolol after 3 months of treatment.[40] However, the ability to compare the current data with this meta-analysis is limited by multiple factors, including differences in baseline IOP and study design. Of note, a recent head-to-head phase 2 clinical trial compared the IOP-lowering efficacy of LBN to latanoprost in patients with primary open-angle glaucoma and OAG. A statistically significant additional IOP lowering of 1.2 mm Hg was observed for LBN over latanoprost at 28 days.[29]

In conclusion, the findings of this study demonstrate that LBN 0.024% once daily in the evening is noninferior to timolol 0.5% administered twice daily and results in significantly greater IOP lowering over 3 months of treatment in subjects with OAG or OHT. In addition, LBN 0.024% treatment resulted in a significantly greater reduction in mean diurnal IOP than timolol 0.5% over the course of the study. LBN was well tolerated overall and exhibited a safety profile typical of topical prostaglandin analogue therapy.

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