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

The APOLLO Study

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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

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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