ORIGINAL RESEARCH

Retrospective Chart Review on Real-World Use of Latanoprostene Bunod 0.024% in Treatment-Naïve Patients with Open-Angle Glaucoma

Constance O. Okeke · Eitan S. Burstein · Valerie Trubnik ·

James E. Deom · Michael S. Cooper · Desirae A. Brinkley ·

J. James Thimons · Alexander J. Kabiri · Kerry M. Gelb

ABSTRACT

Introduction: The objective of this study was to evaluate real-world effectiveness of latanoprostene bunod (LBN) ophthalmic solution 0.024% in treatment-naïve patients newly diagnosed with open-angle glaucoma (OAG) or ocular hypertension.

C. O. Okeke (✉)
Virginia Eye Consultants/CVP, Norfolk, VA, USA
e-mail: iglaucoma@gmail.com

E. S. Burstein
Connecticut Eye Consultants/Danbury Eye Physicians and Surgeons, Danbury, CT, USA

V. Trubnik
OCLI, Manhasset, NY, USA

J. E. Deom
Hazleton Eye Specialists, Hazle Township, PA, USA

M. S. Cooper
Solinsky EyeCare, West Hartford, CT, USA

D. A. Brinkley
Eye Specialty Group, Memphis, TN, USA

J. J. Thimons
Ophthalmic Consultant of Connecticut, Fairfield, CT, USA

A. J. Kabiri
Malik Eye Associates, Manhattan, NY, USA

K. M. Gelb
Contact Lens and Vision, Woodbridge, NJ, USA

Methods: This multicenter retrospective chart review included patients aged ≥ 18 years, with no history of medical, laser, or surgical intraocular pressure (IOP)-lowering intervention and at least two follow-up visits (spanning ≥ 2 months) following initiation of LBN treatment. Extracted data included age, sex, race, cup-to-disk ratio, central corneal thickness, IOP, visual acuity (VA), concomitant medications, and adverse events. In patients treated bilaterally, the eye with the higher baseline IOP was the study eye.
Results: Medical charts for 65 patients (mean [SD] age, 59 [14] years; 53.8% female) encompassing 125 eyes treated with LBN were reviewed across nine clinical sites. Mean (SD) IOP at baseline was 21.7 (5.9) mmHg. Mean days to first and second follow-up visit were 43 and 141, respectively. LBN use resulted in a mean (SD) reduction from baseline of 7.1 (4.7) and 7.3 (5.1) mmHg at the first and second follow-up visits, respectively ($P < 0.0001$ for both). Reductions among patients with IOP > 21 mmHg ($n = 30$) at baseline were 10.0 (4.5) and 11.1 (4.6) mmHg at the first and second follow-up visits ($P < 0.0001$ for both). There were no meaningful changes in VA. Adverse events appeared infrequent, with only one report of ocular redness.
Conclusion: In this real-world, retrospective chart review, LBN 0.024% use resulted in robust IOP lowering in newly diagnosed OAG patients new to treatment, and appeared well tolerated.

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Key Summary Points
Why carry out the study?
Latanoprostene bunod ophthalmic solution (LBN) 0.024% is a nitric oxide-donating prostaglandin analog demonstrated in clinical trials to lower intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension.
This retrospective medical chart review evaluated the IOP-lowering efficacy of LBN in patients newly diagnosed with OAG known to be treatment-naïve, a population not specifically evaluated in clinical trials.
What was learned from the study?
In the overall data set (n = 65 patients), LBN treatment resulted in mean IOP lowering of 31% in treatment-naïve OAG patients with a mean baseline IOP of 21.7 mmHg; percent IOP lowering was 41% and 22% in the subsets of patients with baseline IOP > 21 mmHg and ≤ 21 mmHg, respectively.
While prospective studies are warranted to confirm these findings, these data support the use of LBN in OAG patients naïve to therapy.

DIGITAL FEATURES

This article is published with digital features to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12962819.

INTRODUCTION

Glaucoma is a progressive optic neuropathy affecting approximately 2.9 million people in the United States and a leading cause of irreversible blindness worldwide [1–3]. While the etiology of glaucoma is multifactorial, intraocular pressure (IOP) is currently the only modifiable risk factor for glaucoma [3–5]. Intraocular pressure is determined by the balance between aqueous humor secretion by the ciliary body and its drainage via the trabecular meshwork (TM)/Schlemm's canal and uveoscleral pathways [3, 5, 6]. In glaucoma, dysfunction of the TM/Schlemm's canal pathway leads to increased resistance to outflow and thus elevated IOP. Elevated IOP, in turn, can cause biomechanical stress at the optic nerve head, leading to a loss of retinal ganglion cells and vision [3–5]. Although glaucoma is typically associated with elevated IOP, or ocular hypertension (OHT), it can also develop when IOP is in the normal range (10–21 mmHg) [3]. Lowering IOP has been proven to slow the progression of glaucomatous optic nerve injury and visual field loss in both OHT-associated glaucoma and normal-tension glaucoma (NTG) [7–14].

Latanoprostene bunod (LBN) ophthalmic solution 0.024% (Vyzulta®; Bausch+Lomb; Bridgewater, NJ, USA), which was granted US marketing approval in 2017, is a nitric oxide (NO)-donating prostaglandin F2α analog for lowering IOP in patients with open-angle glaucoma (OAG) or OHT [15–18]. Unlike other IOP-lowering monotherapies, LBN provides a novel dual mechanism of action for improving aqueous humor outflow by targeting the uveoscleral pathway through the action of latanoprost acid and targeting the TM/Schlemm's canal through the action of NO [19, 20]. The latter action is important given the central role of the TM/Schlemm's canal in aqueous humor outflow along with the observation of decreased NO levels in the aqueous humor and in plasma of glaucoma patients [21–25].

The clinical efficacy and safety of LBN 0.024% in subjects with OAG or OHT has been established in multiple trials, including two double-masked, pivotal phase 3 studies that

included an open-label safety extension phase [26, 27]; a 1-year open-label phase 3 study in Japanese subjects [28]; a phase 2 dose-ranging study [29]; a 24-h phase 2 study [30]; and a 24-h phase 1 study in healthy Japanese subjects [31]. In phase 3 studies, LBN led to a mean IOP reduction of up to 9 mmHg from baseline in subjects with OHT or OAG with elevated IOP [26, 27] and a reduction in IOP of 22% from baseline in subjects with low baseline IOP at 4 weeks of treatment, sustained though a year [28]. Additionally, LBN given once daily was shown to be non-inferior [27] or superior [26] to treatment with timolol maleate 0.5% given twice daily in the two phase 3 pivotal trials and resulted in significantly greater IOP reductions when compared to treatment with latanoprost 0.005% in the dose-ranging study [29].

The clinical development program for LBN 0.024% yielded extensive data regarding its IOP-lowering effect in subjects with a wide range of baseline pressures. Yet, given the strict protocol-driven enrollment criteria used in these trials, the larger population that stands to benefit from LBN treatment may as yet not be fully defined. Real-world observational studies, such as medical chart reviews, can provide clinicians with timely insight on the potential effectiveness of new treatments in patient populations encountered in clinical practice but not specifically included in clinical trials—for example, those with a different disease severity or those with comorbidities. Such studies can also help inform the design of further, prospective controlled studies. The majority of the subjects in prior LBN 0.024% phase 2 and 3 clinical studies had a documented history of prior IOP-lowering therapy. While these studies also included subjects who had no history of having received IOP-lowering therapy for the 30 days prior to start of LBN treatment, the study designs generally did not permit determination of whether subjects were truly treatment-naïve. The aim of this real-world, retrospective chart review, then, was to evaluate the potential effectiveness of LBN as initial therapy for patients newly diagnosed with OAG or OHT who were naïve to any IOP-lowering intervention including pharmacotherapy and laser or incisional surgery.

METHODS

Study Design and Patients

This was a retrospective, multicenter medical chart review conducted at nine US ophthalmology and optometry sites. Data reflecting the routine care and follow-up of eligible patients were collected. The study protocol was reviewed by the Advarra Institutional Review Board (Columbia, MD, USA), which granted a waiver of informed consent and exemption from ongoing IRB oversight. All subject data were de-identified and kept confidential in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice [32]. No patient identifying information was recorded or retained.

Patient charts were eligible for review if the patient met the following criteria: aged 18 years or older; newly diagnosed with OAG or OHT; no history of previous IOP-lowering medications or IOP-lowering laser or surgical procedures; prescribed LBN as their initial IOP-lowering treatment; confirmed use of LBN through clinical notes; and at least two follow-up visits (spanning at least 2 months) following initiation of treatment with LBN. Given IRB exemption was obtained on May 6, 2019, the second follow-up visit had to occur prior to this time. Charts of all cases meeting eligibility criteria were identified by staff personnel at each study site. A clinical research associate visited each site and entered the chart data into secure, electronic case report forms. Data extracted from the charts included age, gender, race/ethnicity, diagnoses, cup-to-disk ratio (CDR), central corneal thickness, IOP, visual acuity (VA), adverse events (AEs), and concomitant medications. To confirm the patient was treatment-naïve, charts were inspected as to any evidence of glaucoma treatment (medical or surgical) prior to diagnosis and LBN treatment. Referral records were also evaluated to verify that patients were treatment-naïve. The chart data abstraction period encompassed a time immediately prior to diagnosis of OAG or OHT or, if not available, the visit during which OAG or OHT was diagnosed (baseline visit; i.e., the last visit at which

IOP was measured before initiating LBN treatment) and continued through a minimum of two follow-up visits following commencement of LBN therapy.

Outcomes

Clinical endpoints included changes in IOP, VA, and CDR, use of alternative or adjunctive IOP-lowering medications, AEs, and discontinuation of therapy due to AEs. The primary outcome evaluated was the change in IOP from baseline. The proportions of patients achieving an IOP reduction $\geq 20\%$, $\geq 25\%$, $\geq 30\%$, $\geq 35\%$, and $\geq 40\%$ from baseline (i.e., responder rates) at the first and second follow-up visit were also determined. For each patient, the eye with the higher pretreatment IOP was designated the study eye. If the pretreatment IOP was the same for both eyes, then the right eye was designated the study eye.

Statistical Analysis

Paired t tests were used to compare IOP (one-tailed), VA (two-tailed), and CDR (two-tailed) at baseline and after treatment with LBN. All other endpoints were reported using descriptive statistics. Changes in IOP and responder rates were evaluated in the overall population as well as in subgroups of patients with IOP > 21 mmHg and IOP $\leq$ 21 mmHg at baseline [3, 33]. Primary efficacy analyses were based on the study eye. As additional supportive analyses, endpoints were evaluated in treated fellow eyes where indicated.

Linear regression models were constructed to identify which variables were statistically related to the change in IOP from baseline to follow-up visit 1 and follow-up visit 2, respectively. Potential explanatory variables considered for both models were baseline IOP, the number of days from the baseline visit to follow-up visit 1 (or 2), the patient's age, and binary indicator variables for male, White, Black, Hispanic, and Asian. For each model, only variables with P values for coefficients of less than 0.05 were retained.

Adverse events were summarized using descriptive statistics. Due to the lack of detail in the charts as to whether ocular AEs occurred in one or both eyes and, if one eye, which one, ocular AEs were summarized at the patient level. Where known, AEs reported for untreated fellow eyes were not counted.

Statistical analyses were conducted with Statistix 10 (Analytical Software, Tallahassee, FL, USA) or GraphPad Prism version 6.07 for Windows (GraphPad Software, La Jolla, CA, USA).

RESULTS

Patients

Data for 125 eyes (N = 65 patients) treated with LBN 0.024% were reviewed across nine clinical sites. Among the charts, the earliest baseline IOP evaluation was conducted in December 2017, whereas the latest was conducted in March 2019. The mean (standard deviation [SD]) age of patients was 59 (14) years, 22 (33.8%) were White, and most (53.8%) were female (Table 1). The majority, or 70.8%, of patients were diagnosed with primary OAG (ICD-10 code H40.11), 13.8% were diagnosed with OAG with borderline findings (H40.01), 7.7% with low-tension glaucoma (H40.12), 3.1% as glaucoma suspect (H40.00), 1.5% with both primary OAG and low-tension glaucoma, and 1.5% with OHT (H40.05). No diagnostic code was recorded for 1.5% of patients (Table 1). All but five patients had glaucoma/OHT bilaterally and were treated with LBN bilaterally. Some patients were prescribed additional non-IOP lowering ocular medications (n = 2 lifitegrast, n = 3 loteprednol etabonate 0.5%, n = 1 loteprednol etabonate 0.2%, n = 3 cyclosporine, n = 1 olopatadine); with few exceptions these were utilized for the management of concurrent dry eye disease. Medical comorbidities specified in patient charts were systemic hypertension (n = 25, 38.5%), diabetes (n = 17, 26.2%), and cardiovascular disease (n = 5, 7.7%). Systemic medications included atorvastatin (n = 13, 20.0%), amlodipine (n = 10, 15.4%), aspirin (n = 7; 10.8%), losartan (n = 7, 10.8%), metformin (n = 7, 10.8%), and lisinopril (n = 6; 9.2%).

Table 1 Patient demographics and clinical characteristics

	Patients (N = 65)
Age (years), mean (SD)	59.3 (14.4)
Gender	
Male, n (%)	30 (46.2)
Female, n (%)	35 (53.8)
Ethnicity	
White	22 (33.8)
Black/African American	13 (20.0)
Hispanic	9 (13.8)
Asian	5 (7.7)
Not recorded	16 (24.6)
ICD-10 diagnosis[a]	
POAG	46 (70.8)
OAG with borderline findings	9 (13.8)
Low-tension glaucoma	5 (7.7)
Glaucoma suspect	2 (3.1)
POAG and low-tension glaucoma	1 (1.5)
Ocular hypertension	1 (1.5)
Not recorded	1 (1.5)
Baseline value in study eye	
IOP (mmHg), mean (SD)	21.7 (5.9)
CDR,[b] mean (min, max)	0.6 (0.15–0.9)
CCT (μm),[c] mean (SD; min, max)	547 (58.4; 420–716)

CCT central corneal thickness, *CDR* cup-to-disk ratio, *ICD* International Statistical Classification of Diseases, *IOP* intraocular pressure, *POAG* primary open-angle glaucoma, *SD* standard deviation

[a] Corresponding ICD-10 codes utilized in the medical charts were: POAG (H40.11), OAG with borderline findings (H40.01), low-tension glaucoma (H40.12), glaucoma suspect (H40.00), ocular hypertension (H40.05)

[b] n = 53

[c] n = 34

The study eye, defined as the eye with the higher IOP at baseline, was the right eye in 34 patients (52.3%) and the left eye in the remaining 31 patients (47.7%). The majority of sites used applanation tonometry to measure IOP, with a Tono-Pen used at a single site, and the method of IOP measurement used for each patient was consistent across visits. No IOP was recorded at follow-up visit 1 for two patients; these patients were included in all outcome analyses with the exception of IOP outcomes at visit 1. Mean (SD) IOP at baseline was 21.7 (5.9) mmHg in the study eye and 19.7 (5.5) mmHg in the treated fellow eye. Baseline CDR was recorded for 53 patients (81.5%), with the method noted for two (spectral domain ocular coherence tomography). Mean CDR was 0.6 (min = 0.15, max = 0.9) in the study eye and 0.6 (min = 0.2, max = 0.9) in the treated fellow eye. Central corneal thickness was recorded at baseline for approximately half of patients, while visual fields (all showing mild field loss) were recorded for only six patients.

All patients were prescribed LBN 0.024% therapy once a day to be administered in the evening following their baseline visit. Medical records from six patients included notations that they were not adherent to the LBN dosing regimen (i.e., regularly missing dosages). The mean time (SD) between the baseline visit and the first and second follow-up visit was 43 (41) and 141 (76) days, respectively. The timing of IOP measurement at each visit varied, with an overall mean difference of 2 h 35 min between the patients' earliest IOP measurement and latest IOP measurement.

IOP Lowering at Each Visit

Treatment with LBN 0.024% resulted in a mean (SD) IOP of 14.7 (4.1) mmHg (n = 63) at follow-up visit 1 and 14.4 (3.2) mmHg (n = 65) at follow-up visit 2 in the study eye. The mean (SD) reduction in IOP from baseline was 7.1 (4.7) and 7.3 (5.1) mmHg at the first and second follow-up visit, respectively (P < 0.0001 for both; Fig. 1). Corresponding mean (SD) percent reductions were 30.8 (17.2) % at the first and 30.8 (17.1) % at the second follow-up visit. The degree of IOP lowering in patients whose IOP was measured with a Tono-Pen (n = 13) was consistent with that for the overall data set.
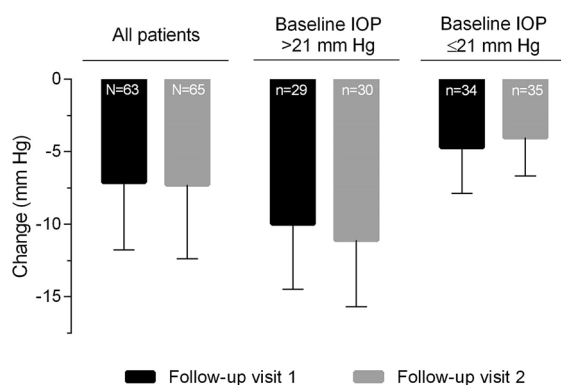
Fig. 1 Change in intraocular pressure overall and by baseline IOP. *IOP* intraocular pressure. *P* < 0.0001 for all changes from baseline

Mean (SD) IOP in the subset of patients with higher IOP (> 21 mmHg; *n* = 30) was 26.7 (4.6) mmHg at baseline and 16.7 (4.5) mmHg and 15.6 (3.6) mmHg at follow-up visits 1 and 2, respectively. Mean (SD) reductions in IOP within this subset of patients were 10.0 (4.5) and 11.1 (4.6) mmHg at the first and second follow-up visit, respectively (*P* < 0.0001 for both vs. baseline) with corresponding mean (SD) percent reductions of 37.1 (13.8) % and 40.9 (13.4) % at the two follow-up visits.

Mean (SD) IOP for the subset of patients with lower IOP (≤ 21 mmHg; *n* = 35) at baseline was 17.4 (2.8) mmHg at baseline and 12.9 (2.8) mmHg and 13.4 (2.4) mmHg at visits 1 and 2, respectively. Among these patients, mean (SD) IOP reductions were 4.7 (3.2) and 4.0 (2.6) mmHg at the first and second follow-up visit, respectively (*P* < 0.0001 for both vs. baseline), which corresponded to mean (SD) percent reductions of 25.4 (18.1) % and 22.1 (15.2) %.

A total of 13 patients had data recorded in their charts for a third follow-up visit. The mean (SD) days to visit 3 in these patients was 230 (120). Among these patients, IOP lowering with LBN was sustained through visit 3. The mean (SD) IOP was 21.8 (4.8) mmHg at baseline, decreasing to 14.5 (3.3) mmHg at follow-up visit 1, 14.2 (3.2) at visit 2, and 15.0 (3.2) mmHg at visit 3. Corresponding mean (SD) reductions from baseline were 7.3 (2.5) mmHg at visit 1, 7.5 (4.8) mmHg at visit 2, and 6.8 (3.4) mmHg at visit 3 (*P* ≤ 0.0001 for all).

Analyses of IOP lowering in patients' treated fellow eyes (*n* = 60) were supportive of findings in patients' study eyes, with significant reductions from baseline at follow-up visits in the full data set of fellow treated eyes, as well as in the subset of fellow treated eyes with higher IOP at baseline (*n* = 19) and subset of fellow treated eyes with lower IOP at baseline (*P* < 0.0001 vs. baseline for all, both visits).

Responder Rates

Overall, 50 (79.4%) and 51 (78.5%) patients had at least a 20% reduction from baseline in the study eye IOP at follow-up visits 1 and 2, respectively (Fig. 2). More than half of patients had at least a 30% reduction from baseline at follow-up visit 1 (*n* = 34, 54.0%) and follow-up visit 2 (*n* = 33, 50.8%). More than a quarter of patients had at least a 40% reduction from baseline at follow-up visit 1 (*n* = 17, 27.0%) and follow-up visit 2 (*n* = 18, 28.1%).

At follow-up visit 1, 27 (93.1%) patients with higher baseline IOP (> 21 mg Hg) had at least a 20% reduction from baseline in IOP (Fig. 2). In addition, more than half (*n* = 16, 53.3%) attained an IOP lowering of at least 40% at follow-up visit 2. Among the patients with lower baseline IOP (≤ 21 mmHg), 23 (67.6%) achieved an IOP reduction in the study eye of at least 20% relative to baseline at follow-up visit 1.

Non-responders were defined as having < 10% reduction in study eye IOP from baseline. Six patients appeared to be non-responders at follow-up visit 1, but all but one were responders (≥ 10% reduction in IOP) at follow-up visit 2. Another two patients appeared to be non-responders at follow-up visit 2; of these, one was a responder at follow-up visit 1, while the other had missing IOP data at follow-up visit 1.

Regression Analyses

For the overall data set, the only variable statistically related to the change in IOP in the study eye from baseline to follow-up visit 1 was baseline IOP, with a coefficient of −0.567 (R^2 = 0.5131; *P* < 0.0001), indicating that each added mmHg in baseline IOP was associated
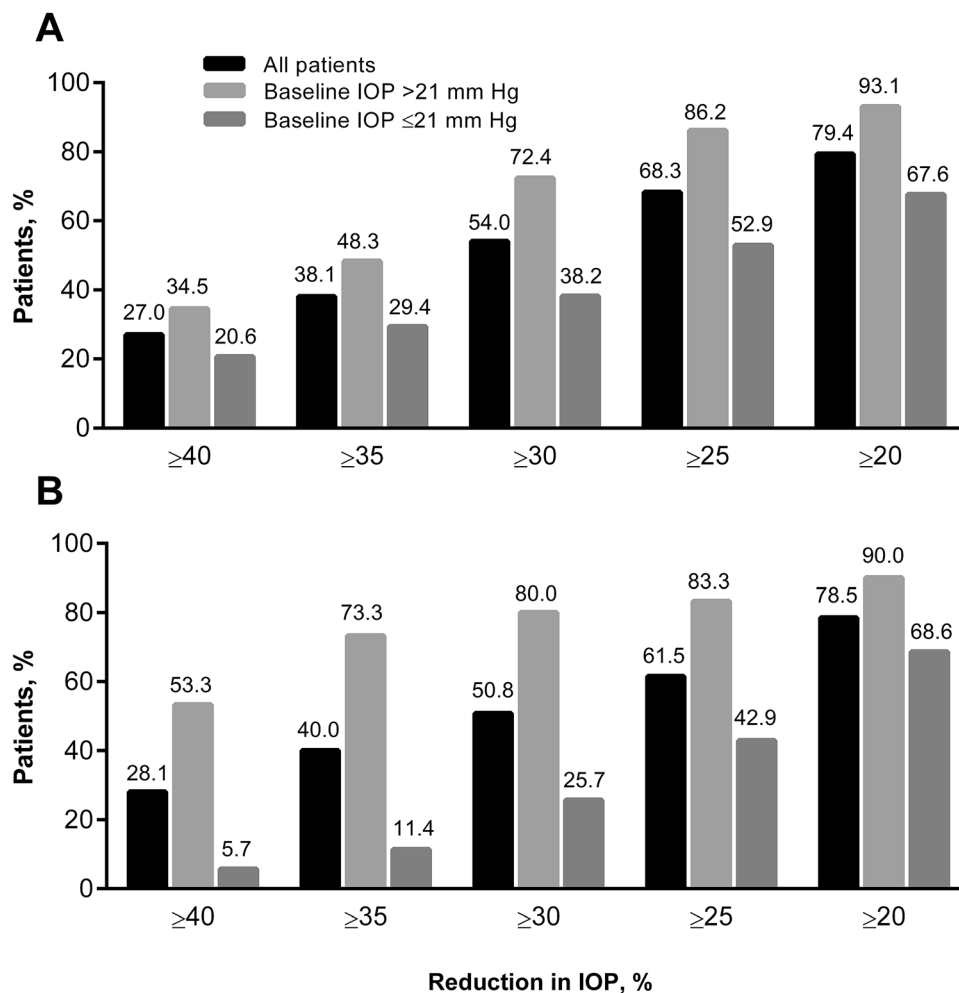
Fig. 2 Percent responders at follow-up visit 1 (**a**) and follow-up visit 2 (**b**). *IOP* intraocular pressure

with a decrease of 0.567 mmHg in IOP at follow-up visit 1. Variables statistically related to the change in IOP in the study eye from baseline to follow-up visit 2 were baseline IOP (coefficient, −0.867; $P < 0.0001$) and follow-up visit 1 IOP (coefficient, 0.339; $P = 0.0008$). The R^2 for the second linear regression model was 0.7679.

Results of regression analysis of data for treated fellow eyes were supportive of results obtained for study eyes data (data not shown).

Safety

There were no systemic AEs recorded in the charts. Overall, 33 patient charts (50.7%) included notations of at least one ocular AE

(Table 2). Common ocular AEs noted in the charts included blurred vision ($n = 10$, 12 events), dryness ($n = 8$, 11 events), itching ($n = 5$, 6 events), irritation ($n = 5$, 6 events), and light sensitivity ($n = 5$, 5 events). Ocular redness was recorded for only one patient, treated unilaterally and only for the study eye. There were no discontinuations recorded due to an AE, nor were there notations as to potential relationship of any AE to treatment(s).

Visual acuity was measured using the same method (typically Snellen) at baseline and follow-up visit 1 for 55 study eyes and at baseline and follow-up visit 2 for 46 study eyes. There were no meaningful changes in VA in the study eye or in the treated fellow eye from baseline to either follow-up visit. Mean VA was 20/39.5

Table 2 Adverse events reported in > 1 patient charts

	All patients (N = 65)	
	n (%)	**Events**
Patients with ≥ 1 AEs[a]	33 (50.8)	70
Specific AEs		
Blurred vision	10 (15.4)	12
Dryness	8 (12.3)	11
Irritation	5 (7.7)	6
Itching	5 (7.7)	6
Light sensitivity	5 (7.7)	5
Burning	4 (6.2)	4
Eye pain	3 (4.6)	4
Tearing	3 (4.6)	3
Change in vision	2 (3.1)	2
Keratitis	2 (3.1)	3
Macular degeneration	2 (3.1)	3

AE reports are limited to those recorded in the charts

AE adverse event

[a] AE reports in eyes not treated with LBN were not counted

(n = 60) at baseline, 20/39.6 (n = 55) at the first visit and 20/37.8 (n = 46) at the second visit for the study eye and 20/29.2 (n = 55) at baseline, 20/27.5 (n = 51) at the first visit and 20/25.6 (n = 44) at the second on treatment visit for the treated fellow eye. One treated fellow eye had a loss of three lines (from 20/20 to 20/40 at both follow-up visits), while no study eyes had a loss of > 2 lines at either follow-up visit.

Cup-to-disk ratio measurements were available at both baseline and follow-up visit 1 for 38 patients and at both baseline and follow-up visit 2 for 35 patients. Study eye mean (standard error) change in CDR ratio from baseline to follow-up visit 1 (−0.00842 [0.0104]) and to follow-up visit 2 (−0.00486 [0.0109]) was not statistically significant for either comparison (P = 0.4227 and P = 0.6584, respectively).

Adjunctive IOP-Lowering Medications and IOP-Lowering Medication Switches

Adjunctive medication use and medication switches are presented in Fig. 3. At their first follow-up visit, two patients at one site were prescribed an additional IOP-lowering medication (netarsudil ophthalmic solution 0.02% [Rhopressa®]) as an adjunct to treatment with LBN. In one patient study eye IOP decreased from 38 mmHg at baseline to 16 mmHg at visit 1, and subsequently decreased another 2 mmHg to 14 mmHg with the addition of netarsudil; in the second patient, study eye IOP decreased from 18 mmHg to 15 mmHg at visit 1 and subsequently decreased another 4 mmHg to 11 mmHg with the addition of netarsudil. Two more patients were prescribed an adjunctive IOP-lowering medication after their second follow-up visit (dorzolamide hydrochloride-timolol maleate ophthalmic solution [Cosopt®] for 1 patient, bimatoprost ophthalmic solution 0.01% [Lumigan®] for the other). However, no further follow-up information was available for these patients at the time of their chart reviews. Seven patients were switched from LBN to another IOP-lowering medication after the second follow-up visit: five to bimatoprost ophthalmic solution 0.01% (two due to cost/insurance coverage, three reason not reported), one to netarsudil plus latanoprost ophthalmic solution 0.005% (reason not reported), and one to travoprost ophthalmic solution 0.004% (due to insurance coverage). One additional patient, noted as being non-adherent to treatment, discontinued LBN at visit 2 and was started on travoprost 4 months later.

DISCUSSION

In this real-world, retrospective chart review in treatment-naïve patients newly diagnosed with OAG or OHT, LBN use resulted in robust IOP lowering and was well tolerated. Treatment with LBN resulted in a mean IOP decrease of 30.8% from baseline to each follow-up visit overall, and as much as 40.9% (at follow-up visit 2) in the subset of patients with higher IOP (> 21 mmHg) at baseline. LBN was also used
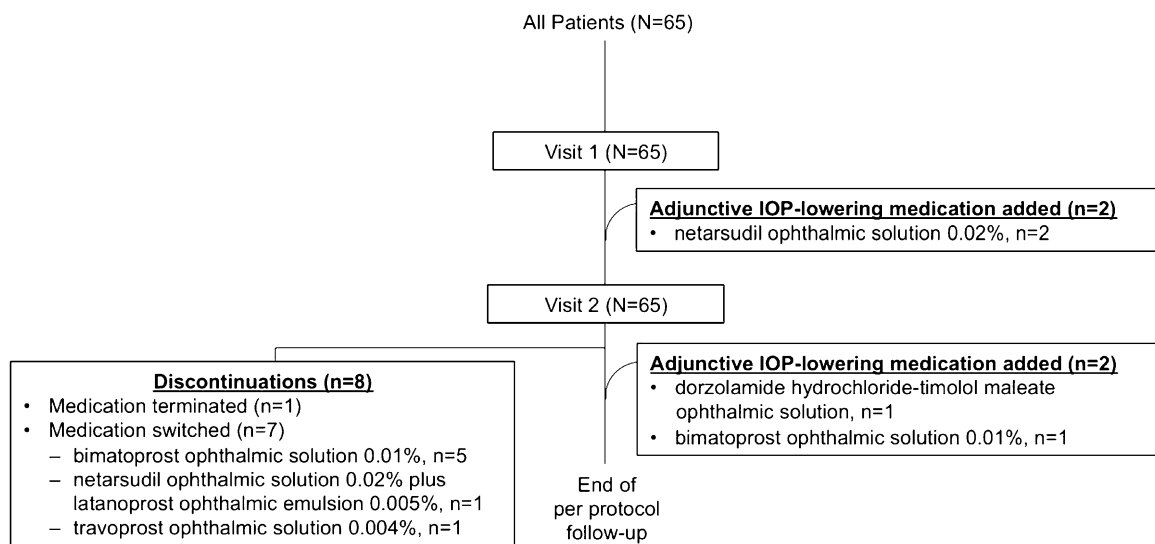
Fig. 3 Concomitant IOP-lowering medications and medication switches. *IOP* intraocular pressure, *LBN* latanoprostene bunod 0.024%

successfully in patients with lower (≤ 21 mmHg) baseline IOP, including those with an NTG diagnosis, with a mean decrease from baseline of 25.4% and 22.1% at the first and second follow-up visits, respectively. In the overall data set and in both subgroups, these IOP decreases were attained by the first follow-up visit (average ~ 1.4 months) persisting through the second follow-up visit (average ~ 4.7 months). A fifth of reviewed patient charts had IOP data for a third follow-up visit (average ~ 7.7 months), and sustained IOP lowering was demonstrated in this subset of patients at this latter visit as well. These findings are consistent with those from previous randomized controlled clinical trials in OAG and OHT subjects, where LBN treatment resulted in a mean diurnal IOP reduction of 32.0% at 3 months in subjects with a baseline IOP of 26.7 mmHg [19, 34], and 22.0% at 4 weeks in Japanese subjects with a baseline IOP of 19.6 mmHg [28], and produced sustained reductions in IOP over 1 year of treatment [19, 28, 34]. The American Academy of Ophthalmology recommends an initial target IOP lowering of 20% to 30% in patients with primary OAG in order to slow disease progression [35]. With respect to attaining such targets, approximately four-fifths of all patients in this chart review achieved a ≥ 20% decrease in IOP at the first and second follow-up visits, and more than half had reductions of at least 30% at each follow-up visit.

Gender, age, race, and the number of days from the baseline visit to follow-up visit 1 or 2 were not associated with changes in IOP over the duration of the study based on linear regression analyses. The only significant predictor of change in IOP was the baseline value. Notably, patients with higher baseline IOP measurements experienced average decreases that were more than twice those of the patients with the lower baseline IOP measurements. The fact that higher baseline IOP was associated with larger changes by follow-up visit 1 and follow-up visit 2 is consistent with previous observations of a correlation between baseline IOP and magnitude of improvement following treatment, and with the concept that subjects with a higher baseline IOP have greater potential for measurable improvement [36, 37].

There were few safety findings in this retrospective chart review. There were no meaningful changes in VA, nor were there any systemic AEs recorded in the charts. Any ocular AEs recorded were infrequent, although the retrospective nature of our study likely led to underreporting of AEs. Further, a number of

patients were under treatment for other pre-existing ocular disease(s), which along with the limited review and abstraction of chart data confounded any inferences regarding these AEs. Notably, eye redness was reported for only one patient, which is consistent with the low incidence of eye redness (5.9% for conjunctival hyperemia and 2.0% for ocular hyperemia) reported in a pooled analysis of data from phase 3 studies of LBN [34]. The low incidence of ocular redness reported with LBN to date stands in contrast to that of other prostaglandin analogs (except latanoprost) as well as to that of Rho kinase inhibitors [38–43].

Many of the subjects in previous pivotal phase 2 and phase 3 clinical studies had received treatment with other IOP-lowering therapies prior to treatment with LBN. Findings from the current study therefore provide evidence, within the limitations of a retrospective analysis, that LBN appears at least as, if not more, effective in newly diagnosed treatment-naïve patients as it is in those with more established disease. We hypothesize that when initiating therapy with LBN in early disease, there may be a greater opportunity than in late-stage disease for the NO-donating moiety released by LBN to relax the tissue of the TM and thus increase aqueous humor outflow [44]. In this regard, it is notable that approximately a third of patients experienced IOP lowering in excess of 40% from baseline. However, further prospective, controlled studies are warranted.

This study is subject to several limitations inherent in its retrospective design and small sample size. While each patient served as his or her own historical control, there was no placebo or active control group. Only one of the 65 patients was diagnosed with OHT. Further, patients who did not use LBN for at least two follow-up visits were excluded from the study, allowing for a potential selection bias toward patients whose experience with LBN was effective and well tolerated. The timing of the IRB approval required patients to have completed two visits prior to May 1, 2019, limiting data from most patients to two follow-up visits only. Although every effort was made to verify that patients included in the analysis were treatment–naïve (i.e., through review of referral

records and medical charts), there remains a small possibility that a few patients had previously received IOP-lowering medications or undergone surgical procedures for glaucoma. Two patients were prescribed an additional IOP-lowering agent at their first follow-up visit, and therefore their IOP results at the second follow-up visit cannot be attributed solely to LBN. Six patients were noted to be non-adherent to LBN treatment, and there were likely others, which would have lowered the degree of mean IOP lowering observed at the follow-up visits. Some patients were on concurrent systemic antihypertensive medications including nitrovasodilators, which in theory may have attenuated IOP lowering with LBN. The real-world nature of the data collection resulted in unavoidable missing data due to incomplete and/or inconsistent charting across sites, although very little data were missing for IOP (two patients with IOP data missing at follow-up visit 1). Although a previous clinical study showed little variation in IOP lowering with LBN during daytime hours [30], the timing of IOP measurements in our study were inconsistent across patients and visits, and IOP findings were therefore likely impacted, to some degree, by fluctuations in diurnal IOP. Data gathering was limited primarily to objective findings, such as IOP measurements, and it was not possible to evaluate more subjective variables such as patient satisfaction with treatment. The practice of recording AEs varied by site, and it is likely that not all were captured within the patient's medical chart, though it is generally presumed that notable AEs would have been recorded. Finally, there was no control over the methods/tools each site used for the measurements of interest (IOP, VA, etc.).

CONCLUSION

The results of this real-world retrospective chart review indicate that LBN provides effective IOP lowering and good tolerability in treatment-naïve patients with OAG regardless of baseline IOP. LBN appeared to be at least as effective in lowering IOP in treatment-naïve patients as in patient populations previously

studied in clinical trials with more established disease, and thus can be considered a suitable treatment option in early-stage OAG patients.

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