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ORIGINAL RESEARCH

Latanoprostene Bunod 0.024% Early Experience Program (LEEP): A Canadian Initiative for Open-Angle Glaucoma and Ocular Hypertension

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ABSTRACT

Introduction: Here we report the intraocular pressure (IOP) changes following treatment with latanoprostene bunod (LBN) 0.024% in patients in Canadian ophthalmology practices.
Methods: This real-world, open-label, 6-week, observational study collected data from 59 Canadian ophthalmologists and a total of 653 patients. Eligibility was open to all patients treated with LBN 0.024% instilled once daily for open-angle glaucoma or ocular hypertension. IOP was assessed prior to initiating LBN and after a planned 6 weeks of treatment. Patient demographics, prior treatment(s), IOP, and patient/physician satisfaction ratings were recorded. Subgroup analyses included (1) patients naïve to prior IOP-lowering medication (with or without prior selective laser trabeculoplasty [SLT]) initiating LBN; (2) patients switching from a pre-existing medication to LBN; and (3) patients adding LBN to existing medications.
Results: Of 653 patients included, 251 were naïve to previous medical antihypertensive therapy, 369 were switched to LBN from a previous medication, and 26 added LBN on top of existing medications (seven patients did not indicate status). Mean baseline IOP was 19.5 mmHg in the overall cohort and follow-up occurred over a period of 37.9 ± 7.9 days. Mean IOP was reduced by 16.3% (95% confidence interval 14.9–17.7) across all included patients. Overall IOP reduction from baseline was largest for naïve patients with no prior SLT (29.3%), with age and baseline IOP key determinants of outcomes in this group. Patient and physician satisfaction scores were high.
Conclusion: This initial Canadian clinical experience of LBN in diverse patient and physician populations reflected its use in a real-world context, and demonstrated a significant

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IOP-lowering effect with LBN across patient groups seen in routine practice. Patient and physician satisfaction scores were high and in notable agreement.

Keywords: Intraocular pressure; Latanoprostene bunod; Open-angle glaucoma; Ocular hypertension; Nitric oxide donor; Patient satisfaction

Key Summary Points

Latanoprostene bunod (LBN) 0.024% is a prodrug with two active metabolites, each of which promotes aqueous humor outflow via independent mechanisms, giving LBN a unique dual mechanism of action for the control of intraocular pressure (IOP), which is a crucial risk factor for glaucoma progression.

This observational study assessed real-world performance of once-daily LBN over a median follow-up of 5 weeks in 653 Canadian patients, including those new to antihypertensive therapy, those switched to LBN from other medications, and those adding LBN onto existing treatment.

The largest IOP reductions between baseline and 6-week follow-up were observed in patients new to antihypertensive therapy but mean IOP was significantly reduced across all included patients.

This real-world assessment of LBN in a diverse patient population demonstrated IOP-lowering benefit across multiple clinical settings with high satisfaction scores from both patients and physicians.

INTRODUCTION

Glaucoma is a chronic condition and is one of the most common causes of blindness worldwide [1, 2]. No cure for glaucoma currently exists, and elevated intraocular pressure (IOP) is a crucial modifiable risk factor for the progression of glaucoma [2]. Large-scale landmark studies demonstrate that patients with glaucoma experience half the risk of progression when appropriately treated with topical antihypertensive medical therapy [3–7]. This equates to an approximate risk reduction of 10–19% for each millimeter of mercury of IOP reduced [8, 9]. Achieving a patient's target IOP might require aggressive treatment, with frequent changes of ocular antihypertensive medication modality, and target IOP should be individualized and often reevaluated on the basis of disease stage, patient risk factors, life expectancy, and social circumstances [10]. It is common for patients to receive multiple ocular antihypertensive approaches to maintain appropriate IOP control, including topical treatments and selective laser trabeculoplasty (SLT), but they may require one of several incisional surgical interventions [11–13].

There are several effective classes of topical antihypertensive medications for glaucoma, including prostaglandin analogues (PGAs), β-blockers, α-adrenergic agonists, and carbonic anhydrase inhibitors [10]. Latanoprostene bunod (LBN) 0.024% is a nitric oxide-donating PGA. As a prodrug, LBN is rapidly activated in the ocular tissues through carboxyl ester hydrolysis into two active metabolites: a nitric oxide-donating metabolite and a prostaglandin F2α analogue metabolite [14]. Each metabolite utilizes an independent mechanism of action to promote aqueous humor outflow, giving LBN a unique dual mechanism of action. The prostaglandin F2α metabolite binds to the F-prostanoid receptor in the ciliary muscle and increases uveoscleral outflow secondary to induced extracellular matrix alterations [15, 16]. The nitric oxide metabolite is thought to increase conventional outflow by eliciting smooth muscle cell relaxation within the trabecular meshwork, Schlemm's canal, and distal outflow pathway [17]. These distinct mechanisms of action are thought to be additive; however, the exact contribution of each metabolite to increasing outflow through the distinct outflow pathways remains under investigation.

Two similarly designed, double-masked, phase 3 randomized studies, each with open-label safety extension phases, established the clinical efficacy and safety of LBN 0.024% in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) [18–20]. An open-label non-comparative clinical trial demonstrated successful IOP control over 1 year of LBN therapy [21], and a phase 2 clinical trial revealed significantly greater IOP-lowering capacity, with LBN, relative to latanoprost [20]. As a result of the LBN PGA metabolite, the side-effect profile and adverse events associated with LBN in these trials would be familiar to the PGA prescribing physician.

Successful management of glaucoma depends largely on treatment initiation and adequate treatment continuation, as for in many other chronic asymptomatic diseases, however, a well-recognized barrier to successful topical antihypertensive therapy is patient adherence [22]. Among patients demonstrating significant visual field progression after 1 year of medical treatment, adherence rates as low as 20% were observed; patients demonstrating stability after 1 year approached 85% adherence [23]. Factors impacting compliance have been well studied [24, 25], and adherence to eye drop medication decreases significantly as the number of individual eye drops a patient is required to administer increases [26].

Postmarketing surveillance complements findings from clinical trials to inform therapeutic choice by considering data from observational cohort studies, case–control studies, and spontaneous reporting of suspected associated adverse events [27]. While less controlled than clinical trials, postmarket patient and physician experience studies can provide insight and information from diverse patient and physician populations, representative of routine clinical practice, and contribute to permanent, ongoing evaluation of a treatment after its approval for use [28]. The purpose of the present study was to observe and report on the integration of the novel topical antihypertensive agent LBN 0.024% into Canadian ophthalmology practices.

METHODS

Study Design

This postmarketing study was a 6-week, open-label, non-controlled, prospective, observational, multicenter study conducted among 59 ophthalmologists to evaluate changes in IOP after initiation of LBN IOP-lowering therapy in patients with OAG or OHT. To ensure the data were closely reflective of routine clinical practice, physicians maintained their normal approach to patient assessments and follow-up appointments.

Anonymized data, from patients who had provided consent for their data to be used for the research, was collected between September 2019 and March 2020. This work followed the Personal Information Protection and Electronic Documents Act, the Good Clinical Practice guidelines of the Declaration of Helsinki and was reviewed and approved by the Ethical Review Committee of University of Toronto.

Study Population

The study enrolled men and women ≥18 years of age, with elevated IOP and a diagnosis of OAG or OHT. Included patients were on three or fewer IOP-lowering agents and either had not achieved their given IOP target with current medical therapy or were well controlled but experiencing significant side effects with current medications. Three distinct patient groups were enrolled: (1) patients starting LBN previously naïve to IOP-lowering medications (with or without previous SLT); (2) patients switching to LBN to replace an existing glaucoma medication; and (3) patients adding LBN on top of current IOP-lowering medications. Patients who recently (last 6 months) enrolled in a clinical trial for an ophthalmic active pharmaceutical ingredient prior to the baseline visit were excluded. To reflect real-world patient populations, no exclusion criteria based on surgical procedures or laser were used for patient selection; recent ophthalmic surgeries, including laser, were not criteria for exclusion.

Treatment

At the investigator's discretion, patients were started on LBN as their first IOP-lowering medication, switched a pre-existing medication for LBN, or added LBN on top of an existing IOP-lowering medication regimen. Patients were provided claim cards to receive the medication free of charge at their pharmacy. Instructions were provided to instill one drop once daily in the affected eye(s), starting the evening after the baseline visit. Patients starting LBN in exchange for an existing glaucoma medication were instructed to discontinue one of their previous medications at the baseline visit and initiate LBN that evening. Patients adding LBN to existing medications were instructed to initiate LBN therapy the evening after the baseline visit, continuing their other IOP-lowering medications as originally instructed.

Data Collection and Analysis

Baseline data collected included age, sex, lens status, diagnosis (OAG/OHT), date of diagnosis, previous laser therapy, date of previous laser therapy, baseline IOP, current IOP-lowering medications, and the reason for switching from an existing medication to LBN (if applicable). Subsequent observations collected after a planned 6 weeks of follow-up included IOP, patient and physician satisfaction scores (on a scale from 0 to 10, where "0" represents strongly dissatisfied and "10" represents strongly satisfied; patients determined their satisfaction with treatment independently of their physician), and qualitative feedback from both patients and physicians. Both eyes were evaluated for each patient.

Data were analyzed using SPSS (IBM). Mean (±standard deviation [SD]) IOP change and IOP percent reduction (IOPR%) between baseline and follow-up visit were calculated for each of the three patient groups. Subgroup analyses were carried out to investigate potential associations between prior laser therapy, the reason for switching to LBN, patient/physician satisfaction ratings, and the magnitude of IOPR% achieved. All statistical tests were performed as two-sided tests with an alpha set at $p \leq 0.05$.

RESULTS

Demographics

A total of 653 patients were enrolled by 59 ophthalmologists across Canada, in the provinces of Ontario ($N=255$), Quebec ($N=151$), Alberta ($N=98$), Saskatchewan ($N=7$), New Brunswick ($N=10$), Nova Scotia ($N=49$), and British Columbia ($N=83$). Baseline characteristics of patients by group and prior SLT status are presented in Table 1. Among included patients, 251 (39%) were naïve to glaucoma medical therapy, 369 (57%) switched to LBN from a prior glaucoma medication, and 26 (4%) added LBN to an existing treatment regimen. The reasons reported for switching to LBN from a previous glaucoma medication are presented in Table 2. Overall, the mean (±SD) follow-up time was 37.9 ± 7.9 days.

Mean baseline IOP was considered low at 19.5 mmHg in the overall cohort, which could reflect the IOP-lowering effect of prior treatment in 382/653 enrolled patients ($N=369$ for the switch group and $N=13$ for the add-on group). The naive patient group had a baseline IOP of 21.4 mmHg; the switch and add-on groups had baseline IOPs of 18.6 and 18.1 mmHg, respectively. There was a significant difference between the naïve and switch treatment groups in follow-up time and baseline IOP; however, the clinical significance of these baseline differences is likely negligible. All patients were followed up for more than 1 week.

Study Outcomes

IOP changes and IOPR% from baseline to the 6-week follow-up visit among the entire study population and each subgroup are presented in Table 3. For all studied patients, over a mean (SD) follow-up period of 37.9 (7.9) days, there was a mean (SD) reduction in IOP of 3.6 (0.9) mmHg. Patient and physician satisfaction scores were high, with mean (SD) scores of 7.8 (2.3) and 7.8 (2.1), respectively (Fig. 1a, b). No

Table 1 Baseline characteristics for the overall, naïve, switch, and add-on patient groups

Baseline characteristics	LBN 0.024%															
	Entire cohort				Naïve				Switch				Add-on			
	All	SLT	No SLT	NS SLT	All	SLT	No SLT	NS SLT	All	SLT	No SLT	NS SLT	All	SLT	No SLT	NS SLT
Patients (*N*)	653[a]	234	339	80	251	44	176	31	369	177	147	45	26	13	9	4
Age																
Mean (years)	67.1	68.5	65.9	68.0	67.2	68.4	66.5	67.6	66.9	68.4	66.1	68.3	69.9	68.6	71.4	83.8
± SD	12.5	11.0	13.7	11.3	11.9	10.3	12.6	11.0	12.9	11.3	13.6	11.6	13.3	12.4	14.7	4.9
Male, *n* (%)	300 (46)	105 (45)	161 (47)	34 (43)	123 (49)	18 (40)	93 (53)	19 (61)	162 (44)	85 (48)	62 (42)	19 (42)	10 (38)	6 (43)	3 (33)	3 (75)
Female, *n* (%)	340 (52)	127 (54)	178 (53)	35 (44)	123 (49)	26 (60)	76 (43)	12 (39)	199 (54)	90 (51)	81 (55)	26 (58)	16 (62)	7 (57)	6 (67)	1 (25)
Phakic, *n* (%)	359 (55)	108 (46)	203 (60)	28 (35)	131 (52)	22 (50)	95 (54)	13 (42)	214 (58)	83 (47)	96 (65)	13 (29)	11 (42)	5 (36)	5 (50)	–
OAG, *n* (%)	529 (81)	211 (90)	258 (76)	58 (73)	201 (80)	37 (83)	148 (84)	27 (87)	299 (81)	166 (94)	110 (75)	38 (85)	22 (85)	12 (93)	7 (75)	4 (100)
OHT, *n* (%)	84 (13)	16 (7)	59 (17)	9 (11)	53 (21)	7 (16)	42 (24)	4 (13)	29 (8)	8 (5)	16 (11)	5 (11)	3 (12)	1 (7)	2 (17)	–
Prior SLT 180°, *n* (%)	–	84 (36)	–		–	13 (30)	–		–	69 (39)	–		–	5 (36)	–	
Prior SLT 360°, *n* (%)	–	105 (45)	–		–	22 (50)	–		–	74 (42)	–		–	7 (57	–	
Baseline IOP																
Mean (mmHg)	19.5	18.6	19.9	19.2	21.4*	18.6	22.0	21.4	18.6*	18.3	20.4	18.6	18.1	18.1	18.2	16.4
± SD	5.3	4.8	5.9	5.5	5.5	3.8	5.7	6.1	4.6	4.7	5.8	5.3	4.7	3.6	5.8	4.5
Follow-up time																
Mean (days)	37.9	37.0	38.4	37.6	36.6*	35.9	36.9	36.7	38.8*	38.0	39.3	38.6	40.3	36.3	46.0	44.0
± SD	7.9	8.2	7.7	7.6	7.6	8.2	7.3	7.3	7.9	8.3	7.7	7.9	9.4	8.2	8.6	10.4

IOP intraocular pressure, *LBN* latanoprostene bunod, *NS* SLT status not stated, *OAG* open-angle glaucoma, *OHT* ocular hypertension, *SD* standard deviation, *SLT* selective laser trabeculoplasty

*$p < 0.05$ naïve vs. switch by one-way analysis of variance

[a]Seven patients did not indicate a status of either naïve, switch, or add-on

Table 2 Prior medication and reasons for switching to LBN in the 369 (57%) patients who switched therapy

	Switch (*N* = 369) %
Prior medication	
Vistitan	22
Latanoprost	21
Travoprost	13
Izba	7
Alphagan	5
Brimonidine	5
Lumigan RC	3
Timoptic XE	2
Travatan	2
Trusopt	2
Alphagan P	1
Monoprost	1
Pilocarpine	0
Timolol	0
Reasons for switching	
Suboptimal IOP control	67
Other	8
Ocular pain/discomfort	10
Hyperemia	10
Ocular allergy	4
Suspected non-compliance	1
Economic reasons	1

IOP intraocular pressure, *LBN* latanoprostene bunod

patients discontinued treatment during the follow-up period for any reason. Among the different administration groups, follow-up IOPs were significantly reduced from baseline in the naïve and switch patient groups (Fig. 1c). Mean IOPs in the add-on group were lower than the overall program baseline; however, the difference, a mean (95% confidence interval [CI]) IOPR% of −14.8% (−20.2%, −9.5%), was not statistically significant. For all included patients, final IOPR% was statistically significant relative to baseline, and the naïve patient group showed a significant difference in IOPR% versus the switch and add-on subgroups (Fig. 1d). Further analysis on the medication-naïve patient population was undertaken to determine if prior SLT had a significant effect on patient outcomes.

Naïve Patients

Patients naïve to IOP-lowering medication (with or without prior SLT) demonstrated a mean (95% CI) IOPR% of −25.6% (−37.0%, −18.0%) and a linear model analysis was performed to determine if prior SLT status had an impact on IOP change from baseline. A total of 251 participants were identified in the database as naïve and of these, 43 patients were removed from the analysis; 31 were removed because they had unknown SLT status, one patient was removed as the criterion for selection was mild-to-moderate IOP and this participant was identified as having severe IOP, and 11 patients were removed because of missing data. Of the 208 participants included in the analysis, 171 did not report prior SLT and 37 reported prior SLT. These patients were followed for a period of between 1 and 6 weeks, with a median follow-up of 5 weeks.

Naïve Patients Without Previous SLT

The results in medication-naïve patients without prior SLT demonstrated the greatest (*N* = 171) IOPR% of 29.3% (21.9–15.4 mmHg). The results showed that the higher the baseline IOP, the greater the magnitude of IOP reduction achieved. Naïve patients without SLT and baseline IOP ≥ 21 mmHg (*N* = 98) had an IOP reduction of 34.3% (mean baseline IOP 25.8 mmHg, mean follow-up IOP 16.9 mmHg) compared with those with a baseline IOP of < 21 mmHg (*N* = 73; mean baseline IOP 16.63 mmHg, mean follow-up IOP 13.44 mmHg), who had an IOP reduction of 19.2% (−3.19 mmHg).

Table 3 Study outcomes by administration group and prior SLT status

Patient group (*n*)	IOP (mmHg)				IOPR% with 95% confidence interval			Satisfaction scores (1–10)			
	Baseline	SD	Follow-up	SD	Change (%)	Upper (%)	Lower (%)	Physician	SD	Patient	SD
All patients (653)	19.5	5.3	15.9	4.3	− 16.3	− 17.7	− 14.9	7.8	2.3	7.8	2.1
SLT (234)	18.6	4.8	16.4	4.7	− 10.6	− 12.9	− 8.3	7.2	2.5	7.8	2.1
No SLT (339)	19.9	5.9	15.6	4.0	− 19.4	− 21.1	− 17.7	8.1	2.1	7.8	2.2
NS SLT (80)	19.2	5.5	15.5	5.0	− 16.7	− 26.4	− 3.6	8.2	2.9	7.2	2.4
Naïve (251[a])	21.4	5.5	15.3	4.2	− 27.5	− 37.0	− 18.0	7.6	2.5	7.8	2.1
SLT (43)	18.6	3.8	14.7	3.1	− 19.9	− 27.5	− 11.5	6.7	2.8	7.8	2.1
No SLT (176)	22.0	5.7	15.4	4.3	− 29.3	− 38.0	− 20.0	8.0	2.2	7.8	2.2
NS SLT (31)	21.4	6.1	16.5	4.2	− 26.4	− 30.6	− 9.3	7.6	2.2	7.8	2.8
Switch (369)	18.6	4.6	15.9	4.3	− 16.7	− 18.6	− 14.9	7.9	2.2	7.8	2.2
SLT (177)	18.3	4.7	16.2	4.8	− 11.2	− 13.9	− 8.3	7.5	2.3	7.7	2.2
No SLT (147)	20.4	5.8	15.8	4.0	− 19.7	− 22.0	− 17.3	8.1	2.1	7.8	2.2
No SLT (45)	18.6	5.3	15.5	4.4	− 15.4	− 26.2	− 6.4	7.1	2.7	7.1	2.4
Add-on (26)	18.1	4.7	15.7	4.8	− 14.8	− 20.2	− 9.5	8.1	2.0	8.0	1.7
SLT (13)	18.1	3.6	15.8	3.2	− 13.8	− 22.1	− 5.5	7.7	2.4	8.1	1.6
No SLT (9)	18.2	5.8	15.5	6.2	− 16.0	− 23.9	− 8.2	8.6	1.5	7.9	2.0
NS SLT(4)	16.4	4.5	13.5	4.5	− 17.4	− 29.2	− 11.3	4.0	–	6.0	–

IOP intraocular pressure, *IOPR*% IOP percent reduction, *SD* standard deviation, *SLT* selective laser trabeculoplasty, *NS SLT* SLT status not stated

[a]One patient excluded by criteria of severe IOP

Naïve Patients with Previous SLT

Medication-naïve patients with a history of SLT ($N=37$) demonstrated a smaller IOPR% of 19.9% at follow-up compared with medication-naïve patients without a history of SLT ($N=171$) IOPR% of 29.3% (SD 15.2; $p<0.001$). A formal analysis was carried out using a linear model with IOP change from baseline comparing both groups matched for covariates such as age, sex, glaucoma diagnosis, ocular hypertension diagnosis, other diagnosis, time since diagnosis, and baseline IOP and the patient's SLT status as the main factor. The results demonstrated that there is no statistically significant difference in the change in IOP between patients with similar baseline IOP with prior SLT and those without prior SLT among medication-naïve patients. Among the selected covariates, only age, where older patients tended to have a greater reduction in IOP, and the baseline IOP, where patients with a higher baseline IOP tended to have a greater reduction in IOP, were considered significant at the 5% level in determining the change in IOP (Fig. 2).

Physician satisfaction scores were significantly lower for patients with prior SLT relative to patients naïve to SLT. However, no significant difference was found in patient satisfaction scores between these two groups.

Switch Patients

Patients switching from another glaucoma medication made up the largest group of patients ($N = 369$), and this group of patients also experienced an important IOPR% with a mean (95% CI) of −16.7% (−18.6%, −14.9%). The most common reason for switching therapies (Table 2) was suboptimal IOP control (67%), followed by ocular pain and discomfort (10%), hyperemia (10%), "other" (8%), ocular allergy (4%), economic reasons (1%), and suspected non-compliance with current therapy (1%).

DISCUSSION

In this postmarket surveillance study, LBN therapy elicited a significant IOP-lowering effect in patients with OAG or OHT. Patients previously naïve to IOP-lowering medical therapy experienced the greatest reduction in IOP from baseline to follow-up, and the reduction was statistically significant. A more modest reduction in IOP was observed in patients who were switched from a previous ocular antihypertensive to LBN as well as patients who added LBN to an existing regimen of ocular antihypertensive medications. Overall, patients who underwent SLT prior to initiating LBN had a lower baseline IOP and experienced smaller IOP reductions, with age and baseline IOP key determinants of outcomes

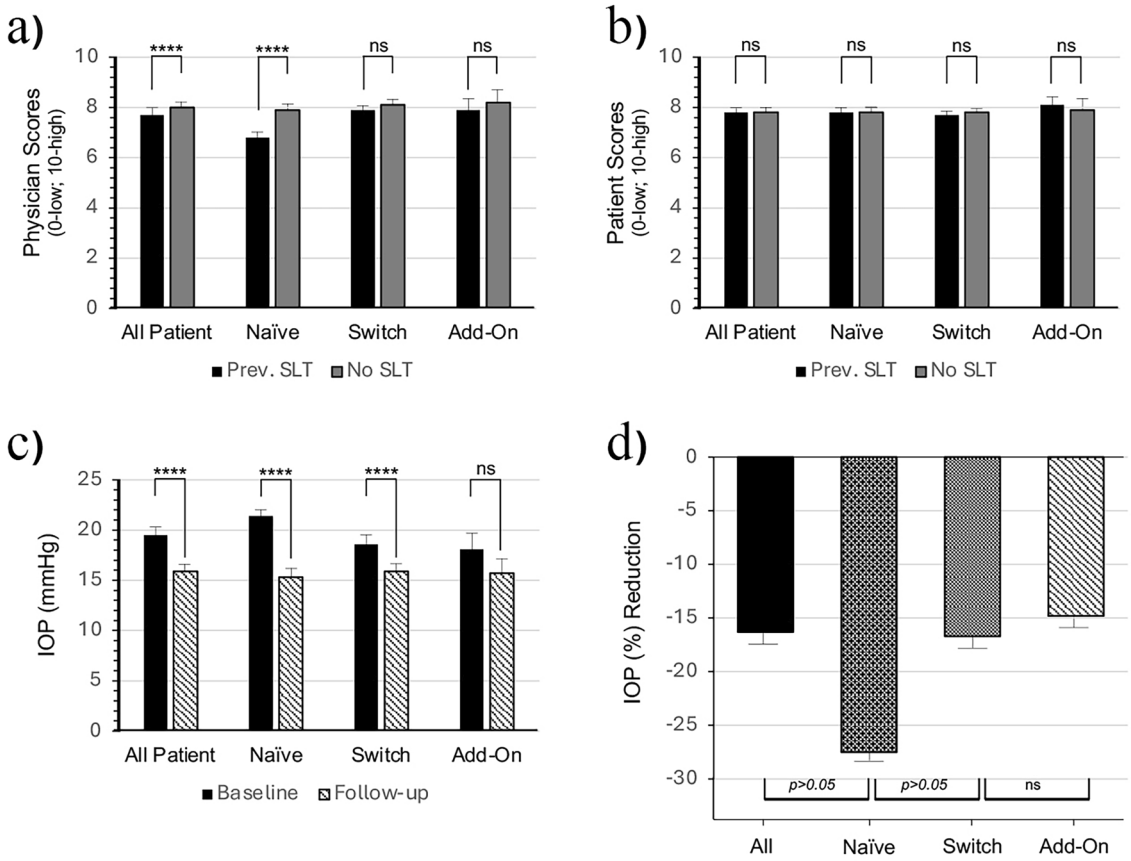

Fig. 1 **a** Physician satisfaction scores and **b** patient satisfaction scores by study group and SLT history. **c** Absolute IOP change from baseline to follow-up visit by study group. **d** IOPR% by study group. ****$p < 0.0001$ by 2-way analysis of variance with multiple comparisons indicated in the figure. *IOP* intraocular pressure, *IOPR*% IOP percent reduction, *ns* not significant, *SLT* selective laser trabeculoplasty

in this group. This was reflected in the reported physician satisfaction scores, which were generally very high but significantly lower for patients with a history of SLT prior to initiating LBN. Patient scores, however, were unaffected by SLT history and were generally quite high.

No studies have previously compared the IOP-lowering effects of LBN 0.024% to placebo; however, a recent network meta-analysis estimated that latanoprost alone induced in a 3.1 mmHg mean reduction in IOP over a 3-month period compared with placebo. That same network meta-analysis reported that LBN achieved a 1.23 mmHg greater reduction in IOP compared with latanoprost alone [29]. Data from the present study are in line with these previous estimates of IOP-lowering capacity and demonstrate IOP reductions of 4.3 mmHg in patients without a history of SLT. Those with a history of SLT demonstrated an approximate reduction of 2.2 mmHg from baseline.

Many studies show that previous topical antihypertensive therapy does not impact the efficacy of subsequent SLT [30–32], with a few notable exceptions [33, 34]. However, the impact of SLT on subsequently initiated medical therapy is much less studied. With recent interest in positioning SLT as a first-line ocular antihypertensive therapy from the LiGHT trial [35], more research is required to understand the potential impact of primary SLT on downstream ocular antihypertensive therapeutic options. It has been suggested that LBN may have lower efficacy after SLT because of the impact of SLT on the trabecular meshwork cells. SLT elicits morphological changes, disrupting intercellular junctions and cytoskeletal processes to ultimately increase outflow capacity [36]. Trabecular meshwork-cell smooth muscle relaxation, as is induced by the nitric oxide-donating metabolite of LBN, may require well-functioning cytoskeletal machinery to increase outflow capacity. Thus, it has been hypothesized that prior SLT cellular alterations may impair the magnitude of cellular relaxation achieved through the nitric oxide-donating metabolite. However, this observational study, based on the linear model analysis conducted between naïve patients with or without prior SLT, demonstrated that when matched for baseline IOP and other covariates, there was no statistical difference in IOP reduction between the two groups.

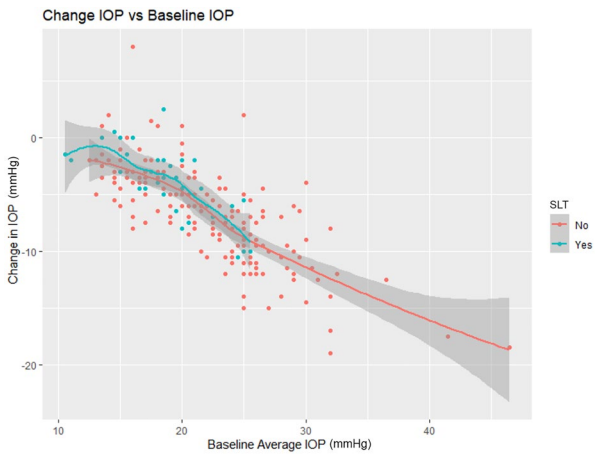

Fig. 2 Naïve patients change in IOP vs. the baseline IOP by SLT status (no previous SLT = "No"; previous SLT = "Yes"). The trends are estimated using the locally estimated weighted scatterplot smoothing (LOWESS). The plot indicates that the baseline IOP range of participants without SLT is larger (11.0–46.5 mmHg) than for participants with SLT (10.5–25.5 mmHg), and that the trends in the overlapping base IOP region in the two groups are similar. *IOP* intraocular pressure, *SLT* selective laser trabeculoplasty

The effect of baseline IOP on medication efficacy has been demonstrated in a wide body of literature on all IOP-lowering medication and is further supported by the results of this trial, in a real-world population with a relatively low baseline IOP (mean 19.5 mmHg). In LEEP, naïve patients without prior SLT with baseline IOP ≥ 21 mmHg had a greater reduction in IOP than those with a baseline IOP < 21 mmHg. In JUPITER, the study population also included patients with normal-tension glaucoma and the majority of eyes had a baseline IOP between 15 and 21 mmHg. At week 52 of daily treatment with LBN, the percent reduction in IOP in study eyes was 26.3%, in line with the 19.18% reduction seen in the IOP < 21 mmHg group of patients in LEEP [21]. The VOYAGER trial included patients with IOP > 22 mmHg and reported reductions in IOP of 34.6% (26.0 to 17.0 mmHg) [20], which were consistent with the observations from LEEP of a reduction in IOP of 34.3% (25.8 to 16.9 mmHg) among

naïve patients without prior SLT with baseline IOP ≥ 21 mmHg.

Patient satisfaction with medical therapy significantly influences their compliance, suggesting that patient dissatisfaction can increase the risk of visual field progression [22]. Data from the present study revealed high patient satisfaction scores comparable to those previously reported for PGA or PGA fixed-combination antihypertensive agents [37, 38]. Considering the reports of moderate hyperemia associated with LBN therapy, these data are reassuring.

Data from this postmarketing physician and patient experience study are strengthened by the large number of ophthalmologists that participated across Canada, capturing a wide diversity of ophthalmologists, glaucoma specialists, and their patient populations. A broad set of inclusion criteria permitted the evaluation of LBN therapy in several distinct real-world patient types: those naïve to previous ocular antihypertensive medications, those switching to LBN from a previous medication, and those adding LBN on to an existing medication regimen. Patients with and without a history of SLT were also analyzed.

Limitations of the current study are those inherent to non-controlled observational studies, including differences in approach between clinics and physicians (including clinic-specific differences in IOP measurement protocols and approaches to timing of follow-up appointments, reflecting routine practice), and any missing data due to patients lost to or missing follow-up visits. The frequency at which missing data occurred, and in which subgroup, is unknown and reflects routine practice, making it a further inherent limitation of the study design. The impact of any missing data points would be more pronounced in smaller subgroups in terms of reducing statistical power and weakening generalizability. Selection bias at the time of enrollment is also a possibility—physicians are less likely to alter the therapeutic regimens of patients whose IOPs are the most stable—thus, the enrolled patients may have less of an inherent capacity to respond to topical antihypertensive agents. Further, there was no washout period in the present study, meaning medication received before switching to LBN may have continued to impact IOP values (latanoprost specifically is known to elicit lasting IOP reductions for up to 5 weeks after cessation of topical therapy), and making longer-term treatment with LBN of interest [39]. It is a distinct possibility that the IOP-lowering data reported in the present study are confounded by the lasting effects of patients' prior ocular antihypertensive medications. This is especially relevant when comparing IOP-lowering data between patients naïve to previous therapy and patients switching to LBN from a prior ocular antihypertensive agent or adding it on to existing medications.

CONCLUSIONS

In a real-world population, LBN 0.024% significantly reduced mean IOP between baseline and follow-up study visits across the entire study population. Of note, prior SLT did not significantly reduce the expected IOP-lowering efficacy of LBN when matched for baseline IOP, and the overall magnitude of IOP reduction achieved was in the therapeutic range and in line with previous estimates of LBN efficacy. No discontinuations of therapy for any reason were reported, and high satisfaction scores were reported by both patients and physicians. LBN 0.024% integrated well within the practices of the 59 participating Canadian ophthalmologists and is an additional option for medical therapy for patients with OAG or OHT, regardless of prior medical or surgical treatment for the condition.

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and were involved in all aspects of manuscript development (study conception and design, data collection, data analysis, data validation and critical interpretation of research findings, drafting of the manuscript, critical review and revision of the drafts, and approval of the final submitted version of the manuscript). All three authors agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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Data Availability. All assessed data are summarized in the manuscript. Raw data are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. David Yan, Cindy M. L. Hutnik, and Paul Harasymowycz report no conflicts of interest.

Ethical Approval. Anonymized data, from patients who had provided consent for their data to be used for the research, was collected between September 2019 and March 2020. This work followed the Personal Information Protection and Electronic Documents Act, the Good Clinical Practice guidelines of the Declaration of Helsinki and was reviewed and approved by the Ethical Review Committee of University of Toronto.

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