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CADTH COMMON DRUG REVIEW

Clinical Review Report

LATANOPROSTENE BUNOD (VYZULTA)

(Bausch Health, Canada Inc.)

Indication: For the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

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Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BCVA	best-corrected visual acuity
CCB	Canadian Council of the Blind
CDR	CADTH Common Drug Review
CNIB	Canadian National Institute for the Blind
CI	confidence interval
DB	double blind
DCT	dynamic contour tonometry
FFB	Foundation Fighting Blindness
GAT	Goldmann applanation tonometer
IOP	intraocular pressure
ITC	indirect treatment comparison
ITT	intention to treat
LBN	latanoprostene bunod
LOCF	last observation carried forward
LogMAR	logarithm of the minimum angle of resolution
LS	least squares
MI	multiple imputation
MIGS	minimally invasive glaucoma surgery
NICE	National Institute for Health and Care Excellence
OAG	open-angle glaucoma
OHT	ocular hypertension
PGA	prostaglandin analogue
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
WDAE	withdrawal due to adverse event
WOCF	worst observation carried forward

Drug	Latanoprostene bunod (Vyzulta), 0.24 mg/mL (0.024% w/v)
Indication	For the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
Reimbursement Request	As per indication
Dosage Form	Sterile topical ophthalmic solution
NOC Date	December 27, 2018
Manufacturer	Bausch Health, Canada Inc.

Executive Summary

Introduction

Glaucoma refers to a group of optic neuropathies that together form the leading cause of irreversible blindness worldwide.[1] Ocular hypertension (OHT) is the most important risk factor for glaucoma. Current consensus among ophthalmologists and optometrists defines normal intraocular pressure (IOP) as between 10 mm Hg and 20 mm Hg; the average is 15 mm Hg, with fluctuations of about 2 mm Hg to 5 mm Hg.[2] OHT is defined as higher-than-normal intraocular pressure in the absence of optic nerve damage or visual field loss.

Glaucoma is characterized by retinal ganglion cell death, which leads to loss of retinal nerve fibres and changes in the optic disc.[2] Untreated, glaucoma results in irreversible loss of visual field and eventual complete loss of vision.[3] As glaucoma progresses, the peripheral visual field is lost, followed by loss of visual acuity and possibly blindness.[3] The 2008–2009 Canadian Community Health Survey – Healthy Aging estimated that 456,533 Canadians had a diagnosis of glaucoma.[4] A meta-analysis of five national surveys estimated that from 2002 to 2003, the self-reported prevalence of glaucoma in Canada was 2.7% among those aged 40 years and older and 11% in those aged 80 years and older.[5]

Patient input submitted for this review, combined with input from a clinical expert, highlights the extensive psychological, physical, and financial burdens associated with glaucoma and the progression of visual impairment. The physical challenges and loss of independence associated with sight impairment, along with constant fear of impending blindness, can paralyze a patient with a sense of powerlessness and lead to anxiety and depression.

The glaucoma clinical practice guidelines published by the Canadian Ophthalmological Society state that lowering IOP is the only clinically established method of glaucoma treatment.[2]

Vyzulta (latanoprostene bunod [LBN] ophthalmic solution, 0.024%) is a prostaglandin F2 alpha analogue that aims to lower IOP. Vyzulta is indicated for the reduction of IOP in patients with OHT or open-angle glaucoma (OAG). Vyzulta is likely to act by increasing the outflow of aqueous humour through both the uveoscleral and trabecular meshwork routes.[6] The recommended dose of Vyzulta is one drop in the conjunctival sac of the affected eye(s) once daily in the evening. If Vyzulta is used concomitantly with other topical ophthalmic drug products to lower IOP, patients are recommended to administer each drug at least five minutes apart.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of LBN 0.024% ophthalmic solution for the reduction of IOP in patients with OAG or OHT.

Results and Interpretation

Included Studies

Two phase III, noninferiority, randomized controlled trials (RCTs) (APOLLO and LUNAR) identified as pivotal trials by the manufacturer were included in this review.[7,8] The primary objective of both trials was to evaluate the noninferiority of LBN 0.024% ophthalmic solution (once daily) compared with timolol maleate 0.5% (twice daily) for mean IOP reduction over three months of treatment at the following nine time points: 8:00 a.m., 12:00 p.m., and 4:00 p.m. each day at week 2, week 6, and month 3. In both trials, patients were randomized in a 2:1 ratio for treatment with LBN 0.024% ophthalmic solution (once daily in the evening) and vehicle (once daily in the morning) or timolol maleate 0.5% (twice daily).

Noninferiority was determined in both APOLLO and LUNAR based on the primary end point if the upper limit of the confidence intervals (CIs) did not exceed 1.5 mm Hg at any of the nine time points and did not exceed 1.0 mm Hg for at least five out of the nine time points. The noninferiority margin was selected by the manufacturer based on discussions with the FDA, historical glaucoma noninferiority studies, and historical data from landmark glaucoma trials.[9]

In APOLLO, the criteria for superiority of LBN 0.024% ophthalmic solution compared with timolol maleate 0.5% was met if noninferiority was determined and if the upper limit of the 95% CI did not exceed 0 mm Hg at any of the nine time points.

APOLLO included a nine-month, open-label, safety extension phase; LUNAR included a three-month, open-label, safety extension phase (described in Appendix 6). A phase III, single-arm, open-label trial (JUPITER) is also summarized in Appendix 6.[10]

In APOLLO, patients were enrolled from 45 sites (N = 284 for LBN 0.024% versus N = 133 for timolol maleate 0.5%) across three countries (Bulgaria, Czech Republic, US). In LUNAR, patients were enrolled from 46 sites (N = 277 for LBN 0.024% versus N =135 for timolol maleate 0.5%) across four countries (Germany, Italy, UK, and US). In both studies, the majority of patients were enrolled from sites in the US, which accounted for 84.8% of the study population in APOLLO and 96.9% in LUNAR. The trials were identical with respect to inclusion and exclusion criteria. Among other criteria, patients were required to have a diagnosis of OAG or OHT in one or both eyes.

APOLLO and LUNAR were limited with respect to the diversity of outcomes assessed in the trials. While the focus on IOP reduction seen in these trials was relevant and consistent with the literature, several other outcomes identified by patients were not assessed as efficacy outcomes. Visual acuity and appearance of the optic nerve were considered as safety outcomes in the trials. Outcomes related to visual field loss, symptoms, health-related quality of life (HRQoL), and vision-related quality of life (VRQoL) were identified as important to patients, but were not assessed in either of the trials; there is insufficient evidence to support a correlation between glaucoma treatment and patient-reported outcomes.[11]

Efficacy

The primary end points for both APOLLO and LUNAR were the IOP in patients' study eyes measured at the following nine time points: 8:00 a.m., 12:00 p.m., and 4:00 p.m. at week 2, week 6, and month 3 (Table 1). In both APOLLO and LUNAR, the least squares (LS) mean IOP in patients' study eyes was numerically lower in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm at all nine time points. In APOLLO, the difference between trial arms was statistically significant across all nine time points. In LUNAR, the difference between trial arms was statistically significant across eight out of nine time points, with the first time point (week 2 at 8:00 a.m.) showing a difference that was not statistically significant.

In APOLLO, the treatment difference between arms ranged from –1.03 mm Hg (95% CI, –0.37mm Hg to –1.6 8mm Hg) to –1.37 mm Hg (95% CI, –0.69 mm Hg to –2.05 mm Hg). In LUNAR, the treatment difference between arms ranged from −0.44 mm Hg (95% CI, 0.26 mm Hg to −1.13 mm Hg) to −1.34 mm Hg (95% CI, −0.72 mm Hg to −1.95 mm Hg).

Noninferiority was determined in both APOLLO and LUNAR, as the upper limit of the CIs did not exceed 1.5 mm Hg at any of the nine time points and did not exceed 1.0 mm Hg for at least five out of the nine time points. In APOLLO, the criteria for superiority of LBN 0.024% ophthalmic solution compared with timolol maleate 0.5% was met, as the upper limit of the 95% CI did not exceed 0 mm Hg at any of the nine time points. In LUNAR, the criteria for superiority were not met due to the treatment difference at the first time point (8:00 a.m., week 2).

In APOLLO, results for the outcome of LS mean change on IOP were consistent with results based on the per-protocol (PP) population and sensitivity analyses using worst observation carried forward (WOCF) and multiple imputation (MI) techniques to impute missing data.

The proportion of patients with IOP reduction greater than or equal to 25% consistently at all nine time points in the first three months was another key secondary end point assessed in both trials. According to the clinical expert consulted for this review, the 25% criterion was deemed to be a clinically meaningful and somewhat conservative threshold. The differences in proportions for this outcome were statically significant in both APOLLO (15.3%; 95% CI, 6.6% to 24.0%; $P = 0.001$) and LUNAR (12.5%; 95% CI, 4.0% to 21.1%; $P = 0.007$), indicating that LBN 0.024% ophthalmic solution is better than timolol maleate 0.5%.

Outcomes related to HRQoL and VRQoL were identified as important to patients but were not assessed in either of the trials. Moreover, there is insufficient evidence to support the correlation between the effects of glaucoma treatment and patient-reported outcomes.[11] Visual acuity assessed through best-corrected visual acuity (BCVA) and the appearance of the optic nerve showed no numerical difference in either trial; however, these outcomes were not assessed statistically, reducing the ability to further interpret the findings. Outcomes related to visual field loss and symptoms of glaucoma were not assessed in either trial.

Harms

In APOLLO and LUNAR, the most common ocular adverse event (AE) in the study eye was related to conjunctival hyperemia and eye irritation (Table 1). In APOLLO, serious adverse events (SAEs) occurred in 1.1% and 1.5% of patients in the LBN 0.024% ophthalmic solution arm and the timolol maleate 0.5% arm, respectively. In LUNAR, SAEs occurred in 2.2% and 0% of patients in the LBN 0.024% ophthalmic solution arm and the timolol maleate 0.5% arm, respectively. Withdrawals due to adverse events (WDAEs) occurred across treatment arms in both trials, with the most common WDAEs related to eye disorders.

Across trials, ocular AEs (in the study eye) occurred more frequently in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm. In LUNAR specifically, differences in ocular AEs relating to conjunctival hyperemia and eye irritation showed a marked increase for those treated with LBN 0.024% ophthalmic solution versus those treated with timolol maleate 0.5%. While there was also an increase seen in APOLLO, it was numerically much smaller than what was observed in LUNAR. Given the identical AE assessment procedures, similar design of the efficacy phase, and similarity in baseline characteristics between the trials, it is unclear why this substantial difference in ocular AEs exists for LUNAR but not APOLLO. The differences in harms outcomes highlight the lack of reproducibility and the uncertainty in the overall findings of the trials.

In comparison with the efficacy phases of APOLLO and LUNAR, no new or cumulative safety concerns emerged from the open-label extension studies. In these safety extensions, the most common ocular treatment-emergent adverse events reported were eye irritation, eye pain, and conjunctival hyperemia.

Potential Place in Therapy[1]

Glaucoma is the leading cause of irreversible blindness globally[12-14] and is estimated to affect 2.7% of Canadians aged 40 years and older.[5] The term glaucoma includes a group of diseases that are broadly classified as open- or closed-angle. Currently the only proven treatment for all types of glaucoma is lowering IOP,[11] which can be done with medication, laser, or surgery.[15] The initial management of glaucoma is usually medically with eye drops. There are currently five classes of medications to manage glaucoma: prostaglandin analogues, beta-blockers, carbonic anhydrase inhibitors, alpha2 adrenergic agonists, and miotics. Some patients are not able to achieve sufficient IOP lowering (often termed target pressure) with the current available medication, due either to lack of efficacy or tolerance and then may progress to interventions such as laser or surgery.[16]

LBN 0.024% ophthalmic solution (Vyzulta) represents a new class of IOP-lowering medication. In addition to acting as a prostaglandin analogue, LBN is expected to release nitric oxide, which is expected to reduce IOP by relaxing the trabecular meshwork and Schlemm's canal to improve outflow. This represents a new mechanism of action that may facilitate IOP lowering in patients who are unable to achieve their target pressure with currently available glaucoma hypotensive medications.

Since all glaucomas are treated by lowering IOP, Vyzulta could potentially be of benefit for both open- and closed-angle glaucomas. The first-line medical therapies for glaucoma,

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

barring any contraindications, are the prostaglandin analogues. This medication class is very effective in lowering eye pressure, easy to use (as they are prescribed for use once a day), and well tolerated. The Ontario Drug Benefit program requires a limited-use form for many glaucoma medications, including the prostaglandin analogues. The limited-use code is to confirm that either the patient was unsuccessful with a beta-blocker or a beta-blocker is contraindicated. Despite this requirement, prostaglandin analogues are usually initiated before a beta-blocker due to the reasons cited previously. However, many patients cannot be controlled with one class of medication; for these patients, adjunctive hypotensive drops are prescribed. The second hypotensive drop is usually a beta-blocker. Additional hypotensive drops are added if a target pressure is not achieved either due to lack of response, insufficient eye pressure reduction, or intolerance. Maximal medical therapy is usually three or four classes of medication. If a patient has not reached their target pressure but is not on three or four classes of medication, either due to intolerance or nonresponse to a medication, then Vyzulta should be considered, as it is a new class of hypotensive drop. Vyzulta would be considered a single drug with two mechanisms of action, and would replace a prostaglandin. It is possible that some ophthalmologists may also consider using Vyzulta as a first-line therapy; however, the high rate of hyperemia may limit widespread us as a first-line drug.

Conclusions

APOLLO and LUNAR were three-month, randomized, double-blind, active-controlled trials that met the inclusion criteria for this review. In both trials, noninferiority (assessed using mean IOP at nine time points) was achieved for treatment with once-daily LBN 0.024% ophthalmic solution compared with twice-daily timolol maleate 0.5%.

Overall, LBN 0.024% ophthalmic solution appeared to be better than timolol maleate 0.5%, with unknown or perhaps only modest clinical implications, while the safety profiles (in terms of eye-related complications) favour timolol maleate 0.5%. Outcomes related to HRQoL and VRQoL were identified as important to patients, but were not assessed in either of the trials.

[redacted]

Ocular AEs occurred more frequently in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm in both trials. In LUNAR, differences in ocular AEs relating to conjunctival hyperemia and eye irritation showed a marked increase for those treated with LBN 0.024% ophthalmic solution compared with timolol maleate 0.5%. While there was also an increase seen in APOLLO, it was numerically much smaller than what is observed in LUNAR.

Table 1: Summary of Results

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% N = 135
IOP				
Baseline – diurnal				
Mean, mm Hg[a] (range)	26.73 (24.0 to 35.7)	26.49 (24.0 to 36.0)	26.61 (24.0 to 35.0)	26.43 (24.0 to 33.5)
Month 3 – diurnal				
Mean (mm Hg)[b]	18.16	19.40	18.13	19.28
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.24 (–1.84 to –0.64)		−1.15 (−1.71 to −0.58)	
Month 3 – diurnal CFB				
Mean, mm Hg[a] (range)	–9.07 (–19.0 to 4.0)	–7.17 (–16.3 to 1.7)	–8.46 (–19.3 to 6.3)	–7.20 (–17.8 to 1.0)
Month 3 at 8:00 a.m.				
Mean (mm Hg)[b]	18.71	19.73	18.68	19.56
Treatment difference[c], adjusted mean[d] (95% CI)[e]	–1.03 (–0.37 to –1.68)		–0.88 (−0.25 to −1.51)	
P value[d]	0.002		0.006	
Month 3 at 12:00 p.m.				
Mean (mm Hg)[b]	17.88	19.15	17.92	19.21
Treatment difference[c], adjusted mean[d] (95% CI)[e]	–1.27 (–0.61 to –1.92)		–1.29 (−0.67 to −1.91)	
P value[d]	< 0.001		< 0.001	
Month 3 at 4:00 p.m.				
Mean (mm Hg)[b]	17.83	19.15	17.72	19.06
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.32 (–0.64 to –2.01)		–1.34 (−0.72 to −1.95)	
P value[d]	< 0.001		< 0.001	
Mean IOP ≤ 18 mm Hg at All 9 Efficacy-Phase Time Points				
N (%)	65 (22.9)	15 (11.3)	49 (17.7)	15 (11.1)
Difference of proportions[f] (95% CI)	11.6 (4.3 to 18.9)		6.6 (−0.4 to 13.5)	
P value[g]	0.005		0.084	
Per Cent Reduction from Baseline in Mean IOP ≥ 25% at All 9 Efficacy-Phase Time Points[h]				
N (%)	99 (34.9)	26 (19.5)	86 (31.0)	25 (18.5)
Difference of proportions[f] (95% CI)	15.3 (6.6 to 24.0)		12.5 (4.0 to 21.1)	
P value[g]	0.001		0.007	
BCVA in the Study Eye[i]				
Baseline				
N	283	135	277	135
Mean (SD)	0.09 (0.137)	0.07 (0.124)	0.09 (0.135)	0.07 (0.119)
Month 3				
N	270	127	261	130
Mean (SD)	0.08 (0.134)	0.07 (0.139)	0.08 (0.121)	0.07 (0.133)

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% N = 135
Optic Nerve[i]				
Baseline				
Normal	249 (88.0)	119 (88.1)	224 (80.9)	104 (77.0)
Abnormal	34 (12.0)	16 (11.9)	53 (19.1)	31 (23.0)
Month 3				
Normal	239 (87.9)	113 (89.0)	211 (80.8)	100 (76.9)
Abnormal	30 (11.0)	14 (11.0)	49 (18.8)	29 (22.3)
Not done	3 (1.1)	0	1 (0.4)	1 (0.8)
Missing	11	8	16	5
New abnormalities on month 3[j]	1 (0.4)	1 (0.8)	0	0
SAEs				
Patients with > 0 SAEs, N (%)	3 (1.1)	2 (1.5)	6 (2.2)[h]	0
WDAEs				
WDAEs, N (%)	4 (1.4)	5 (3.7)	5 (1.8)[i]	1 (0.7)
Deaths				
Number of deaths, N (%)	0	0	0	0
Notable Harms (Study Eye)				
Macular edema	0	0	0	0
Iris hyperpigmentation	0	0	–	–
Conjunctival hyperemia	8 (2.8)	2 (1.5)	25 (9.0)	1 (0.7)
Eye irritation	11 (3.9)	3 (2.2)	20 (7.2)	6 (4.4)
Eye pain	4 (1.4)	3 (2.2)	16 (5.8)	5 (3.7)
Eye dryness	3 (1.1)	1 (0.7)	3 (1.1)	1 (0.7)
Skin pigmentation disorder or hyperpigmentation	1 (0.4)	0	2 (0.7)	0

ANCOVA = analysis of covariance; BCVA = best-corrected visual acuity; CFB = change from baseline; CI = confidence interval; IOP = intraocular pressure; LBN = latanoprostene bunod; mm Hg = millimetre of mercury; SD = standard deviation; SAE = severe adverse event; WDAE = withdrawal due to adverse event.

Note: Harms data include safety population during the efficacy three-month phase.

[a] Derived mean IOP assessment value or derived mean diurnal IOP assessment value, respectively.

[b] Mean was the least squares mean of the mean IOP for the corresponding time point and visit at time-matched overall average baseline under ANCOVA.

[c] Treatment difference = LBN 0.024% ophthalmic solution – timolol maleate 0.5%.

[d] Adjusted means, 95% CIs, and *P* values were from an ANCOVA model, with treatment as a classification variable and time-matched baseline mean IOP as a covariate.

[e] Noninferiority was to be claimed if the upper limit of the CIs was < 1.5 mm Hg at all time points of each visit and < 1.00 mm Hg for at least 5 out of the 9 time points in the efficacy phase. If noninferiority was determined, superiority at each time point was to be claimed if the upper limit of the 95% CI was < 0 mm Hg at all time points of each visit in the efficacy phase.

[f] Difference = LBN 0.024% ophthalmic solution – timolol maleate 0.5%.

[g] The *P* values were from Pearson's chi-squared test.

[h] Per cent reduction from baseline = 100 × (baseline mean IOP – post-baseline mean IOP) ÷ baseline mean IOP.

[i] For two patients, SAEs occurred post-randomization but prior to the administration of the first dose of the study drug; patients still received the drug on day 1 (i.e., these were not treatment-emergent adverse events).

[j] For one patient, WDAE occurred post-randomization, but prior to the administration of the first dose of study drug; the patient did not receive drug.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Introduction

Disease Prevalence and Incidence

Glaucoma is a term that refers to a group of optic neuropathies that together form the leading cause of irreversible blindness worldwide.[1] Ocular hypertension (OHT) is the most important risk factor for glaucoma. Current consensus among ophthalmologists and optometrists is that normal IOP is between 10 mm Hg and 20 mm Hg; the average value of IOP is 15 mm Hg, with fluctuations of about 2 mm Hg to 5 mm Hg.[2] OHT is defined as higher-than-normal IOP in the absence of optic nerve damage or visual field loss. IOP is dependent on the secretion of aqueous humour by the ciliary body as well as on drainage of aqueous humour from the eye through the trabecular meshwork and uveoscleral outflow pathway.[1] The most prevalent type of primary glaucoma in North America is open-angle glaucoma (OAG), in which high IOP is caused by increased resistance to aqueous outflow through the trabecular meshwork.[1] Primary OAG is responsible for more than 70% of glaucoma cases.[3] The other type of primary glaucoma is closed-angle glaucoma, which is characterized by obstruction of the drainage pathways by the iris.[1] Glaucoma can also develop secondary to other conditions (e.g., inflammation, trauma, or pseudoexfoliation), medication usage (e.g., corticosteroids), or ocular surgery.[1,3]

OHT may be present in the absence of glaucomatous damage to the optic disc; only a minority of patients with OHT develop glaucoma.[1-3] However, symptoms of glaucoma may not be apparent until the disease has advanced and caused vision loss. It is estimated that at least half of all people with glaucoma are undiagnosed and not receiving treatment.[1]

Patient input submitted for this review, combined with input from a clinical expert, highlight the extensive psychological, physical, and financial burdens associated with glaucoma and the progression of visual impairment. The physical challenges and loss of independence associated with sight impairment, along with constant fear of impending blindness, can paralyze a patient with a sense of powerlessness and lead to anxiety and depression.

The 2008–2009 Canadian Community Health Survey – Healthy Aging estimated that 456,533 Canadians had a diagnosis of glaucoma.[4] A meta-analysis of five national surveys estimated that from 2002 to 2003, the self-reported prevalence of glaucoma in Canada was 2.7% among those aged 40 years and older and 11% among those aged 80 years and older.[5] Some patients self-reporting glaucoma may have been receiving treatment for OHT as opposed to glaucoma.[2]

Standards of Therapy

The glaucoma clinical practice guidelines published by the Canadian Ophthalmological Society state that lowering IOP is the only clinically established method of treating glaucoma.[2] The guidelines recommend assigning an initial target IOP upper threshold based on the severity of glaucoma, and outline suggestions for upper thresholds along with minimum percentage reductions from baseline IOP.[2] The target IOP should be modified based on a patient's longevity, quality of life, and risk factors for progression.[2]

Treatment strategies for reducing elevated IOP include topical or systemic medications, laser therapy, and surgery.[2] Pharmacologic therapy is the most common method of lowering IOP, and there are several types of drugs available for lowering IOP in patients with OAG or OHT: prostaglandin analogues (PGAs), beta-blockers, carbonic anhydrase

inhibitors, alpha-adrenergic agonists, and direct-acting cholinergic agonists.[2] Of these, the most common first-line therapy involves PGAs due to their favourable effectiveness, once-daily administration, and tolerability compared with the other drugs.[2,17,18] Patients who do not meet their target IOP may receive an additional drug.[2]

Laser trabeculoplasty can be performed as an adjunct to medical therapy when target IOP is not achieved on medication alone.[2] The most common surgical procedure for glaucoma is trabeculectomy, which is employed when both medication and laser trabeculoplasty are not sufficient for achieving target IOP.[2]

Patients with OAG require lifetime therapy, but glaucoma medical therapy is often characterized by nonadherence. Possible reasons for nonadherence include the asymptomatic nature of OHT and early glaucoma, inconvenience of the medication, cost, and adverse side effects.[19]

Drug

Vyzulta (latanoprostene bunod [LBN] ophthalmic solution, 0.024%) is a prostaglandin F2 alpha analogue that aims to lower IOP. Vyzulta is indicated for the reduction of IOP in patients with OAG or OHT. Vyzulta is likely to act by increasing the outflow of aqueous humour through both uveoscleral and trabecular meshwork routes.[6]

The recommended dose of Vyzulta is one drop in the conjunctival sac of the affected eye(s) once daily in the evening. If Vyzulta is used concomitantly with other topical ophthalmic drug products to lower IOP, it is recommended to administer each drug product at least five minutes apart. Vyzulta is supplied as an eye drop dispenser consisting of a natural low-density polyethylene bottle with a dropper tip and turquoise cap in a 7.5 mL bottle with a 5 mL fill volume.

Table 2: Key Characteristics of Vyzulta, Prostaglandin Analogues, and Timoptic

	Latanoprostene Bunod 0.024% (Vyzulta)	Latanoprost 0.005% (Xalatan, Monoprost)	Travoprost 0.004% (Travatan Z, Izba)	Bimatoprost 0.03% (Vistitan) Bimatoprost 0.01% (Lumigan RC)	Timolol maleate 0.5% (Timoptic)
Mechanism of Action	Lowers intraocular pressure by increasing outflow of aqueous humour through both uveoscleral and trabecular meshwork routes.	Selective prostanoid FP receptor agonist. Reduces intraocular pressure by increasing the outflow of aqueous humour.	Travoprost free acid is a highly selective, potent agonist for the FP prostanoid receptor. FP receptor agonists are thought to reduce IOP by increasing the outflow of aqueous humour.	Bimatoprost is a synthetic prostamide analogue and is structurally related to prostaglandin F2alpha. Bimatoprost exhibits no meaningful pharmacological activity at known prostaglandin receptors. Studies suggest that it lowers IOP by increasing uveoscleral and trabecular meshwork outflow.	Timolol maleate is a general beta-adrenergic receptor-blocking drug that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor.

	Latanoprostene Bunod 0.024% (Vyzulta)	Latanoprost 0.005% (Xalatan, Monoprost)	Travoprost 0.004% (Travatan Z, Izba)	Bimatoprost 0.03% (Vistitan) Bimatoprost 0.01% (Lumigan RC)	Timolol maleate 0.5% (Timoptic)
Indication[a]	Reduction of intraocular pressure in patients (Travatan Z: adult patients) with open-angle glaucoma or ocular hypertension. Xalatan may be used for the reduction of intraocular pressure in patients with chronic angle-closure glaucoma who have undergone peripheral iridotomy or laser iridoplasty.				For the reduction of elevated intraocular pressure
Route of Administration	Topical ophthalmic solution				
Recommended Dosage	One drop in the affected eye(s) once daily. Optimal effect is obtained when administered in the evening.				One drop in the affected eye(s) twice a day.
Serious Side Effects/Safety Issues	• Contraindicated in patients with known hypersensitivity to the drug or to any ingredient in the formulation or component of the container (the latter is not mentioned in the Xalatan product monograph). • Should be used with caution in patients with active intraocular inflammation. • Monoprost and Xalatan should be used with caution in patients with herpetic keratitis. • Should be used with caution in patients with a torn posterior lens capsule or known risk factors for macular edema. • Travatan Z, Izba, Vistitan, and Lumigan should be used with caution in patients with aphakia. • May gradually increase the amount of brown pigmentation in the iris, periorbital tissue, and eyelashes in the treated eye. • Eyelashes in the treated eye may increase in length, thickness, and number.				Contraindications: • Hypersensitivity to any component of this product • Reactive airway disease, including bronchial asthma or a history of bronchial asthma; severe chronic obstructive pulmonary disease. • Sinus bradycardia; sick sinus syndrome; sino-atrial block; second- and third-degree atrioventricular block; overt cardiac failure; cardiogenic shock. General: • This drug may be absorbed systemically. • The same types of cardiovascular, pulmonary, and other adverse reactions reported with systemic beta-adrenergic blocking drugs may occur with topical administration.
Other	There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products (not applicable to Monoprost).				

FP = prostaglandin F receptor; IOP = intraocular pressure.

[a] Health Canada indication.

Source: Product monographs for Vyzulta,[6] Xalatan,[20] Travatan Z,[21] Vistitan,[22] Lumigan RC,[23] and Timoptic.[24]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of LND 0.024% ophthalmic solution for the reduction of IOP in patients with OAG or OHT.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Patients with open-angle glaucoma or ocular hypertension Subgroups: • Treatment-naive versus treatment-experienced patients • Baseline disease severity • Baseline IOP
Intervention	Latanoprostene bunod 0.024% ophthalmic solution, one drop to affected eye daily
Comparators	Topical ophthalmic medications for open-angle glaucoma or ocular hypertension: • Prostaglandin analogues (including different formulations of latanoprost, travoprost, and bimatoprost) • Beta-blockers • Carbonic anhydrase inhibitors • Alpha-adrenergic agonists • Direct-acting cholinergic agonists • Combination therapies (e.g., timolol/dorzolamide, timolol/brimonidine, timolol/latanoprost, timolol/travoprost, and timolol/brinzolamide)
Outcomes	Efficacy outcomes: • Intraocular pressure • Visual field loss[a] • Visual acuity[a] • Optic nerve damage • Health-related quality of life[a] • Vision-related quality of life[a] • Symptoms of glaucoma[a] Harms outcomes: • AEs, SAEs, WDAEs, mortality • Notable harms (e.g., macular edema, pigmentation, intraocular inflammation, herpetic keratitis, conjunctival hyperemia, tolerability to medication, DUES, eye irritation, dryness, or pain)
Study Design	Published and unpublished phase III and IV RCTs

AE = adverse events; DUES = deepening of upper eyelid sulcus; IOP = intraocular pressure; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid; Embase (1974–) via Ovid; and PubMed. The search

strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was the drug name (Vyzulta/latanoprostene bunod).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on December 20, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on April 10, 2019. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters):

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- databases (free)
- Internet search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4. Excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

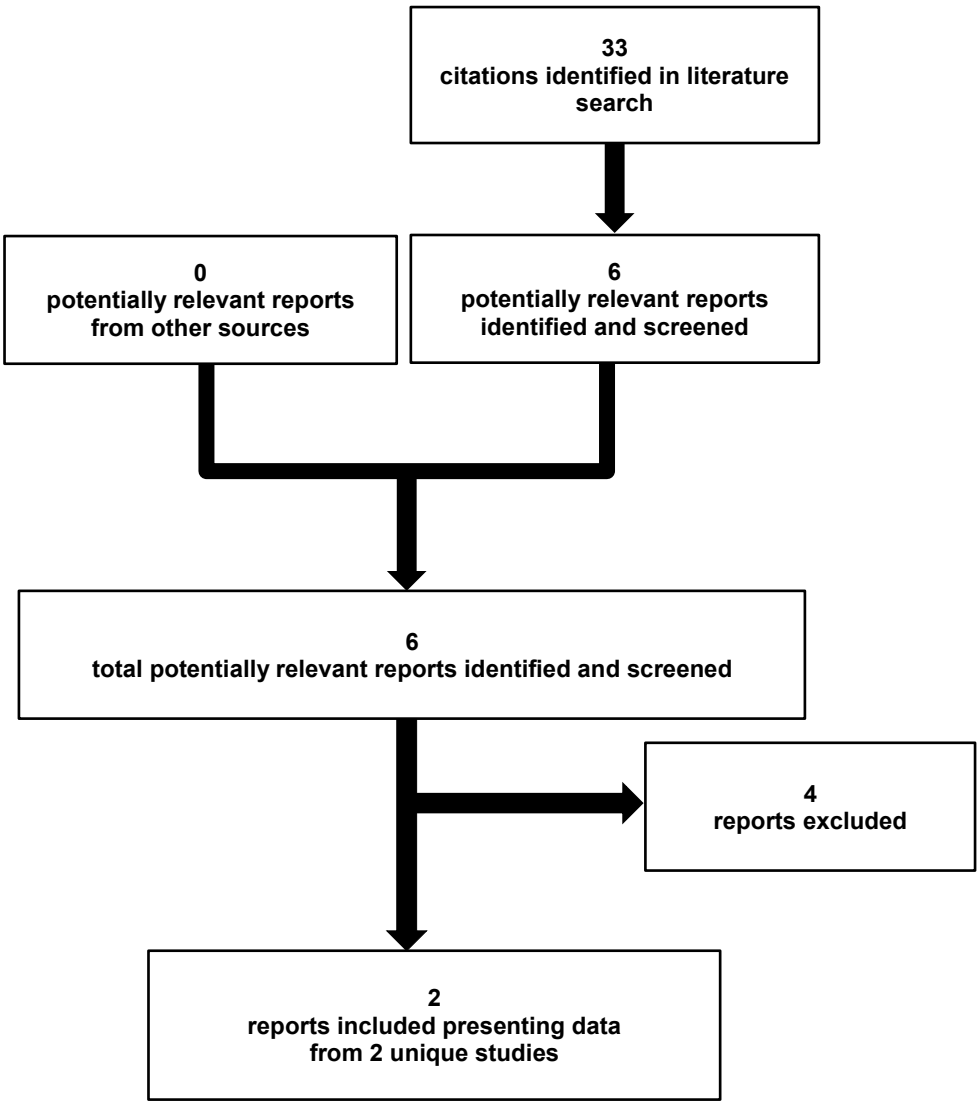


Table 4: Details of Included Studies

		APOLLO	LUNAR
Designs and Populations	**Study design**	DB, parallel-group, double-masked, NI RCT	
	Locations	Bulgaria, Czech Republic, US	Germany, Italy, UK, US
	Randomized (N)	420	420
	Inclusion criteria	• Age 18 years or older ○ Diagnosis of OAG (including pigmentary or pseudoexfoliative) or OHT in 1 or both eyes (based on previous medical history including but not limited to: intraocular pressure measurement, gonioscopy, changes in the optic nerve, changes in the retina, and visual field changes) • At day 1: mean/median IOP ≥ 26 mm Hg at a minimum of 1 time point, ≥ 24 mm Hg at a minimum of 1 time point, and ≥ 22 mm Hg at 1 time point in the same eye, and IOP ≤ 36 mm Hg at all 3 measurement time points in both eyes • BCVA of +0.7 LogMAR units (equivalent to Snellen 20/100) or better in either eye	
	Exclusion criteria	General • Previous exposure to LBN • Severe asthma, severe dysfunction of the liver or the kidneys, wasting disease Ocular • Subjects who were unable to discontinue contact lens use or other eye drop medications (such as artificial tears) during and for 15 minutes following instillation of study drug • Central corneal thickness > 600 µm in either eye • Advanced glaucoma with a cup/disc ratio greater than 0.8, a history of split fixation, or a field loss threatening fixation in either eye • Aphakia, previous or active corneal disease, history of severe dry eye, history of optic disc hemorrhage, history of central/branch retinal vein or artery occlusion, or history of macular edema in either eye. Surgery • Ocular laser surgery, incisional ocular surgery, or severe trauma in either eye within 3 months of screening	
Drugs	**Intervention**	LBN 0.024% q.d., ophthalmic solution	
	Comparator(s)	Timolol maleate 0.5% b.i.d., ophthalmic solution	
Duration	**Phase**		
	Run-in	33 to 28 days	
	Double-blind	3 months	
	Follow-up	9 months (open-label safety extension)	3 months (open-label safety extension)
Outcomes	**Primary end point**	IOP at 8:00 a.m., 12:00 p.m., and 4:00 p.m. at visit 4 (week 2), visit 5 (week 6), and visit 6 (month 3)	
	Other end points	Proportion of patients with IOP ≤ 18 mm Hg consistently at all 9 time points in the first 3 months Proportion of patients with reduction ≥ 25% consistently at all 9 time points in the first 3 months	
Notes	**Publications**	Weinreb et al., 2016[25]	Medeiros et al., 2016[26]

BCVA = best-corrected visual acuity; b.i.d. = twice daily; CDR = CADTH Common Drug Review; DB = double blind; IOP = intraocular pressure; LBN = latanoprostene bunod; LogMAR = logarithm of the minimum angle of resolution; NI = noninferiority; OAG = open-angle glaucoma; OHT = ocular hypertension; q.d. = once daily; RCT = randomized controlled trial.

Note: Two additional reports were included (CDR submission[27] and Health Canada's reviewers report[28]).

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Included Studies

Description of Studies

Two phase III, three-month randomized controlled trials (RCTs) were identified and included in this systematic review (APOLLO and LUNAR).[7,8] The two trials were identical in design except that APOLLO included a nine-month, open-label safety extension phase and LUNAR included a three-month, open-label safety extension phase (described in Appendix 6). A Japanese phase III, single-arm, open-label trial (JUPITER) is also summarized in Appendix 6.[10]

APOLLO and LUNAR

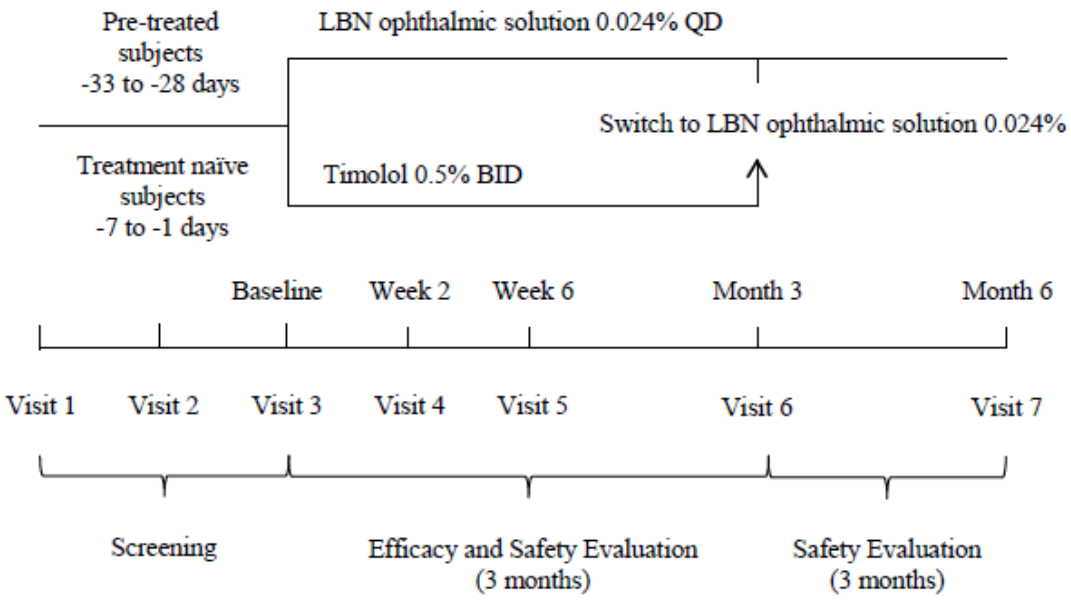
APOLLO and LUNAR were multi-centre, double-masked, parallel-group, noninferiority, active-controlled, manufacturer-sponsored RCTs. The studies included patients from sites in the US and Europe, but not from Canadian sites. The primary objective of both trials was to evaluate the noninferiority of LBN 0.024% ophthalmic solution (once daily in the evening) compared with timolol maleate 0.5% (twice daily, morning and evening) for the assessment of mean IOP reduction at nine time points over three months of treatment. The randomization schedule for each study was created using computer-generated schedules in SAS. Patients in APOLLO and LUNAR were randomized in a 2:1 ratio for treatment with LBN 0.024% ophthalmic solution (N = 286 and 283, respectively) and timolol maleate 0.5% (N = 134 and 137, respectively).

In APOLLO, patients were enrolled from 45 sites across Bulgaria, Czech Republic, and the US. In LUNAR, patients were enrolled from 46 sites across Germany, Italy, UK, and the US. In both studies, the majority of patients were enrolled from sites in the US, which accounted for 84.8% of the study population in APOLLO and 96.9% in LUNAR. APOLLO took place between January 31, 2013 and June 2, 2015, while LUNAR took place between January 28, 2013 and November 26, 2014. Patients enrolled in both trials were treated for three weeks; afterward, patients were followed in an open-label safety extension phase during which they received LBN 0.024% ophthalmic solution (once daily) for nine months in APOLLO and three months in LUNAR.

Figure 2 shows a visual representation of the study design for LUNAR.

In both trials, study treatments were administered in a double-masked manner. The investigator and Bausch Health, Canada Inc. personnel involved in the conduct of the study were fully masked to the randomization order. IOP operators were also masked to patient assignment. Patients were blinded to the treatment, with those receiving once-daily LBN 0.024% ophthalmic solution also receiving treatment with a vehicle identical to the investigational product but without LBN.

Figure 2: Study Design for LUNAR



BID = twice daily; LBN = latanoprostene bunod; QD = once daily.

Source: Clinical Study Reports for LUNAR.[8]

Populations

Inclusion and Exclusion Criteria

The study populations in APOLLO and LUNAR consisted of patients aged 18 years and older. Patients were required to have a diagnosis of OAG (pigmentary or pseudoexfoliative) or OHT in one or both eyes based on a medical history including but not limited to: IOP measurement, gonioscopy, changes in the optic nerve, changes in the retina, or visual field changes. Patients using IOP-lowering medications were required to undergo a washout period (five days for miotics and oral or topical carbonic anhydrase inhibitors; 14 days for alpha and alpha or beta agonists; 28 days for beta-antagonists; 28 days for PGAs). In addition, after washout, patients were required to have a mean or median IOP greater than or equal to 26 mm Hg at a minimum of one time point, greater than or equal to 24mm Hg at a minimum of one time point, and greater than or equal to 22 mm Hg at one time point in the same eye. Patients were also required to have an IOP less than or equal to 36 mm Hg at all three measurement time points in both eyes. Patients were included in the studies if they had a best-corrected visual acuity (BCVA) of +0.7 logarithm of the minimum angle of resolution units (LogMAR) (equivalent to Snellen 20/100) or better in either eye. Patients were excluded if they had a history or current presence of a number of disorders including but not limited to: severe dysfunction of the liver or the kidneys, wasting disease, angina pectoris not controlled by medical or surgical treatment, or severe asthma.

Baseline Characteristics

The baseline characteristics were balanced between arms for each study. Across studies, males represented 41.5% to 42.1% of patients within treatment arms, and the majority were white. The mean age of patients ranged from 63.1 to 65.0 years. The majority of patients

were treatment-experienced. About 25.0% to 29.5% had no documented IOP-lowering medication in their medical histories 30 days prior to visit 1. The derived mean IOP at baseline ranged from 26.43 mm Hg to 26.73 mm Hg. For the study eye, the mean corneal thickness ranged from 546.27 µm to 551.18 µm; the refraction sphere ranged from –0.430 diopters to –0.919 diopters; and the refraction cylinder ranged from 0.13 diopters to 0.366 diopters. The BCVA ranged from 0.7 LogMAR to 0.9 LogMAR, and the optic nerve appeared normal in 77.0% to 88.0% of patients across treatment arms.

Table 5 summarizes the baseline characteristics for APOLLO and LUNAR.

Table 5: Summary of Baseline Characteristics

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% N = 133	LBN 0.024% N = 278	Timolol Maleate 0.5% N = 136
Age, years, mean (SD)	64.7 (10.32)	63.1 (11.23)	65.0 (9.77)	64.1 (9.71)
Male, n (%)	118 (41.5)	56 (42.1)	116 (41.7)	57 (41.9)
Race, n (%)				
White	217 (76.4)	108 (81.2)	204 (73.4)	89 (65.4)
Black/African American	64 (22.5)	24 (18.0)	69 (24.8)	46 (33.8)
American Indian/Alaskan Native	0	0	1 (0.4)	0
Asian	1 (0.4)	1 (0.8)	4 (1.4)	1 (0.7)
Native Hawaiian/Pacific Islander	0	0	0	0
Other	2 (0.7)	0	–	–
Ethnicity, n (%)				
Hispanic or Latino	30 (10.6)	13 (9.8)	36 (12.9)	19 (14.0)
Not Hispanic and not Latino	254 (89.4)	120 (90.2)	242 (87.1)	117 (86.0)
Treatment-naive,[a] n (%)	83 (29.2)	34 (25.6)	82 (29.5)	34 (25.0)
Derived diurnal IOP,[b] mean (range)	26.73 (24.0 to 35.7)	26.49 (24.0 to 36.0)	26.61 (24.0 to 35.0)	26.43 (24.0 to 33.5)
Study eye				
Mean corneal thickness (µm), mean (SD)	546.27 (31.72)	549.64 (31.10)	550.17 (31.11)	551.18 (32.67)
Refraction sphere (diopters), mean (SD)	–0.45 (2.57)	–0.76 (2.63)	−0.919 (2.78)	−0.430 (2.21)
Refraction cylinder (diopters), mean (SD)	0.13 (1.05)	0.25 (1.06)	0.366 (1.05)	0.256 (1.10)
BCVA (LogMAR), mean (SD)	0.09 (0.137)	0.07 (0.124)	0.09 (0.135)	0.07 (0.119)
Optic nerve				
Normal	249 (88.0)	119 (88.1)	224 (80.9)	104 (77.0)
Abnormal	34 (12.0)	16 (11.9)	53 (19.1)	31 (23.0)

BCVA = best-corrected visual acuity; IOP = intraocular pressure; LBN = latanoprostene bunod; LogMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

[a] A patient was considered treatment-naive if he or she did not require a washout period (i.e., had no documented IOP-lowering medication in their medical history 30 days prior to visit 1).

[b] Derived = derived mean IOP assessment value or derived mean diurnal IOP assessment value, respectively.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Interventions

In APOLLO and LUNAR, patients received treatment with one drop per eye of LBN 0.024% ophthalmic solution (once daily in the evening at approximately 8:00 p.m.) and vehicle (once daily in the morning at approximately 8:00 a.m.) or treatment with one drop per eye of timolol maleate 0.5% twice daily (at approximately 8:00 a.m. and 8:00 p.m.). The vehicle was identical to LBN 0.024% ophthalmic solution, but did not contain LBN. For study purposes, the vehicle was used once daily because timolol is taken twice daily while LBN is used once daily. It was buffered to the same pH (5.5) and contained the same preservative (benzalkonium chloride 0.02%).

Concomitant medications could be used if they were not expected to interfere with the study parameters as assessed by the investigator. Throughout the trial, patients were prohibited from using other topical or systemic medications for OHT or OAG and from modifying or initiating systemic or topical medications known to affect IOP, including beta-adrenergic antagonists, alpha-adrenergic agonists, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, and angiotensin II receptor blockers. They were also prohibited from using medications that could affect the safety or efficacy of a NO-donating compound (e.g., vasodilators, such as isosorbide dinitrate and isosorbide dinitrate/hydralazine hydrochloride) and diclofenac.

Outcomes

Across the two trials included in this review, several end points relating to IOP were assessed. IOP was measured using a Goldmann applanation tonometer (GAT) calibrated in accordance with the manufacturer's instructions. GAT produces reliable IOP readings, is identified as the gold standard in measuring IOP,[29] and is recommended for such by both the Canadian Ophthalmological Society glaucoma guidelines and National Institute for Health and Care Excellence (NICE) glaucoma guidelines.[2,17,30,31] IOP was measured in the right eye followed by the left eye, with IOP measured prior to pupillary dilation. The dial was set at 10 mm Hg and adjusted to take the reading. The procedure was conducted two times per eye consecutively. The mean of the two readings was recorded if the readings were within 2 mm Hg of each other. If the two readings were further apart than 2 mm Hg of each other, a third consecutive reading was taken and the median IOP was recorded. In both trials, the IOP operators were masked to the patients' treatment assignment. The study eye was identified as the eye that qualified based on the inclusion criteria at day 0. If both eyes qualified, the eye with the higher mean diurnal IOP at day 0 was considered the study eye. If both eyes had the same mean diurnal IOP, the right eye was considered the study eye.

The primary end point for APOLLO and LUNAR was the IOP in patients' study eyes measured at the following nine time points: 8:00 a.m., 12:00 p.m., and 4:00 p.m. at week 2, week 6, and month 3.

The proportion of patients with IOP less than or equal to 18 mm Hg consistently at all nine time points in the first three months was a key secondary end point.

The proportion of patients with IOP reduction greater than or equal to 25% consistently at all nine time points in the first three months was another key secondary end point.

While not specified in the protocol, subgroup analysis based on prior treatment status was performed for the primary and two secondary end points in both APOLLO and LUNAR.

The BCVA and the appearance of the optic nerve were relevant outcomes that were considered safety end points in the trials. The BCVA was assessed using a standard procedure beginning with a test at four metres. For patients reading 19 or fewer letters correctly at four metres, a test at one metre was performed. The optic nerve was assessed for abnormalities using ophthalmoscopy. Outcomes related to visual field loss, health-related quality of life (HRQoL), and vision-related quality of life (VRQoL) were not included in the trials.

Statistical Analysis

In both APOLLO and LUNAR, the sample size was calculated based on a noninferiority test of the difference between the IOP for those treated with LBN 0.024% ophthalmic solution compared with timolol maleate 0.5% in the per-protocol (PP) population. An estimated 393 patients were required to achieve 90% power (two-sided alpha of 0.05) using a noninferiority margin of 1.5 mm Hg and a standard deviation (SD) of 3.75 mm Hg. [redacted] The assumption for the SD was based on data from a phase IIb trial for LBN 0.024% ophthalmic solution and from a previous study for timolol maleate 0.5%. The 1.5 mm Hg noninferiority margin was selected based on discussions with the FDA, historical glaucoma noninferiority studies, and historical data from landmark glaucoma trials.

The primary end point of IOP of the study eye at nine time points (8:00 a.m., 12:00 p.m., and 4:00 p.m. at week 2, week 6, and month 3) was analyzed using analysis of covariance (ANCOVA) based on the intention-to-treat (ITT) population. The ANCOVA was modelled with fixed-effect terms for baseline IOP and treatment group. Missing data were imputed using the last observation carried forward (LOCF) method at each time point. Treatment with LBN 0.024% ophthalmic solution was compared with timolol maleate 0.5% at each time point using the least squares (LS) means. The results were presented with two-sided 95% confidence intervals (CIs) and *P* values. Noninferiority was determined if the upper limit of the CIs did not exceed 1.5 mm Hg at all nine time points and did not exceed 1.0 mm Hg for at least five out of the nine time points. Superiority was determined if noninferiority was determined and if the upper limit of the 95% CI did not exceed 0 mm Hg at all nine time points. The superiority analysis was planned in advance. Sensitivity analyses were performed for the primary end point using the worst observation carried forward (WOCF) and multiple imputation (MI) methods for the imputation of missing data.

If noninferiority was determined for the primary end point, then the secondary end points were assessed. The two secondary end points (for the proportion of patients with IOP less than or equal to 18 mm Hg consistently at all nine time points in the first three months and the proportion of patients with IOP reduction greater than or equal to 25% consistently at all nine time points in the first three months) were assessed using categorical data analysis. The proportion of patients who met the end point were presented with the difference in proportions, two-sided 95% CIs, and *P* values using Pearson's chi-squared test. Multiplicity due to these additional two end points was adjusted for using the Hochberg method.

In both trials, the main analyses for the primary and secondary end points were repeated with the PP population. An exploratory subgroup analysis was performed for prior treatment status (pre-treated patients compared with treatment-naive patients, where treatment-naive patients were defined as those who did not require a washout [i.e., had no documented IOP medications in their medical history 30 days prior to visit 1]).

Analysis Populations

APOLLO and LUNAR included the following four analysis populations:

- The ITT population included all randomized patients who were treated with at least one dose of the study drug and had both a baseline and at least one post-baseline IOP assessment.
- The PP population included all patients in the ITT population who remained in the study through month 3, had all nine post-baseline IOP assessments, and had no major protocol deviations. Analyses performed on the PP population were according to the treatment they received.
- The randomized population included all randomized patients.
- The safety population included all randomized patients who were treated with at least one dose of the study drug. Analyses performed on the safety population were according to the treatment they received.

Patient Disposition

The proportion of patients that discontinued the trial was similar between treatment arms in both APOLLO and LUNAR. In APOLLO, 7.0% to 7.5% of patients discontinued the efficacy phase. Similarly, in LUNAR, 6.8% to 5.9% of patients discontinued the efficacy phase. Across both trials, the most common protocol violation was that the patient's visit fell outside the visit window. This occurred for 26.9% of patients in APOLLO and 24.0% of patients in LUNAR, and occurred slightly more frequently in the timolol maleate 0.5% arm. Table 6 presents the patient disposition for APOLLO and LUNAR.

Table 6: Patient Disposition

	APOLLO		LUNAR	
	LBN 0.024%	Timolol Maleate 0.5%	LBN 0.024%	Timolol Maleate 0.5%
Screened, N	679		756	
Randomized, N	286	134	283	137
Discontinued efficacy phase,[a] N (%)	20 (7.0)	10 (7.5)	19 (6.8)	8 (5.9)
Discontinued entire study,[a,b] N (%)	34 (12.0)	23 (17.3)	25 (9.0)	11 (8.1)
Withdrew consent	9 (3.2)	4 (3.0)	3 (1.1)	2 (1.5)
Lost to follow-up	2 (0.7)	1 (0.8)	1 (0.4)	1 (0.7)
Adverse event	7 (2.5)	8 (6.0)	5 (1.8)	4 (2.9)
Investigator decision	2 (0.7)	2 (1.5)	1 (0.4)	0
Failure to follow the required study procedures	3 (1.1)	2 (1.5)	6 (2.2)	2 (1.5)
Other	11 (3.9)	6 (4.5)	9 (3.2)	2 (1.5)
ITT, N	284	133	278	136
PP, N	192	80	183	87
Safety, N	283	135	279	136

ITT = intention to treat; LBN = latanoprostene bunod; PP = per-protocol.

[a] Discontinued from ITT population.

[b] Entire study comprises the efficacy and safety phases.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Exposure to Study Treatments

The mean treatment duration was between 88.8 days and 91.4 days across all treatment arms in both APOLLO and LUNAR (Table 7). The majority of patients completed between 56 and 124 days of treatment, with 95.8% and 93.3% of patients in the LBN ophthalmologic solution 0.024% arm and timolol maleate 0.5% arm, respectively, in APOLLO. In LUNAR, 93.2% and 96.3% of patients in the LBN ophthalmologic solution 0.024% arm and timolol maleate 0.5% arm, respectively, completed treatment within this range.

Table 7: Summary of Exposure to Study Drug

	APOLLO		LUNAR	
	LBN 0.024%	Timolol Maleate 0.5%	LBN 0.024%	Timolol Maleate 0.5%
Duration (days) of exposure, mean (range)	89.7 (1, 117)	89.4 (6, 117)	88.8 (4, 133)	91.4 (8, 106)
Treatment duration, n (%)				
Completed 1 to ≤ 28 days	5 (1.8)	5 (3.7)	11 (3.9)	4 (2.9)
Completed 29 to ≤ 55 days	7 (2.5)	4 (3.0)	7 (2.5)	1 (0.7)
Completed 56 to ≤ 124 days	271 (95.8)	126 (93.3)	260 (93.2)	131 (96.3)
Completed ≥ 125 days	–	–	1 (0.4)	0

LBN = latanoprostene bunod.

Note: Duration of exposure (days) = (last known date of drug intake in that phase – first dose date in that phase +1); or if date of last study drug intake was not known, = (last visit date in that phase – first dose date in that phase +1).

Note: Safety population.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Exposure to other medications during the trial was balanced between treatment arms in both APOLLO and LUNAR, with 91.1% to 94.3% of patients taking at least one concomitant medication over the course of the combined efficacy and safety phase. Concomitant drug treatments used by patients throughout the trials are presented in Table 8.

While it is known that 70% to 75% of patients were treatment-experienced and were taking IOP medications that required washout (e.g., PGAs, beta-antagonists, alpha and alpha/beta agonists), aggregate data categorized by medication type used prior to the trials were not available. Prior medications used were only available as individual patient data.

Table 8: Concomitant Drug Treatments

[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Critical Appraisal

Internal Validity

APOLLO and LUNAR were multi-centre, double-masked, parallel-group, noninferiority, active-controlled, manufacturer-sponsored RCTs. Randomization was performed using appropriate methodology with adequate allocation concealment. Baseline and demographic characteristics were generally well balanced across the treatment arms in both trials, indicating successful randomization. Both APOLLO and LUNAR used optimal doses of LBN ophthalmic solution and timolol malate according to a dose-finding study and their respective product monographs.[6,24,32]

In both trials, patients were disallowed from modifying or initiating medications known to affect IOP (e.g., beta-adrenergic antagonists, alpha-adrenergic agonists, calcium channel blockers, ACE inhibitors, and angiotensin II receptor blockers). Throughout the trials, patients' concurrent use of these medications was recorded; for example, approximately 13% to 15% of patients had been concurrently taking beta-blocking drugs. While the distribution of these IOP-affecting medications was similar between trial arms, the impact of taking such medications likely biased the results toward the null, enhancing the likelihood of achieving noninferiority.

In the LUNAR trial, differences in ocular adverse events (AEs), specifically relating to conjunctival hyperemia and eye irritation, show a marked increase for those treated with LBN 0.024% ophthalmic solution compared with timolol maleate 0.5%. While there was also an increase seen in APOLLO, it was numerically much smaller than what was observed in LUNAR. It is unclear why there was such a marked difference between the trials. In both trials, discontinuations over the course of the efficacy and safety phases of the studies were greater in the timolol malate 0.5% arms. This impact, caused by differential discontinuations, is likely to have created an actual study population that differed from the baseline population that was initially balanced with respect to baseline IOP measures.

Both APOLLO and LUNAR were noninferiority trials based on the primary end point of IOP of the study eye at nine time points. The results for all analyses were presented appropriately with two-sided 95% CIs and *P* values. IOP was measured using a GAT. GAT produces reliable IOP readings, is identified as the gold standard in measuring IOP,[29] and is recommended for such by both the Canadian Ophthalmological Society glaucoma guidelines and NICE glaucoma guidelines.[2,17,30,31] The two key secondary end points related to IOP were assessed with adjustment for multiplicity (i.e., Hochberg method). Beyond the analysis of the primary and key secondary end points, subsequent end points (e.g., diurnal IOP, change from baseline IOP) were at risk of inflated type 1 errors as multiplicity was not adjusted for. Relevant sensitivity analyses were performed for the primary end point using the WOCF and MI methods instead of LOCF to impute missing data. The MI method assumes that the data are missing at random; however, it is unclear if this assumption is upheld. The WOCF method is more conservative than the LOCF method. Together, these sensitivity analyses are useful, as they show no deviations from the main analysis based on the LOCF. The proportion of patients with missing IOP data was not provided; therefore, the extent of the missing data and the distribution of missing data by treatment group are unclear. For the primary and key secondary end points, analysis was performed using the PP population.

[redacted]

The large number of protocol violations in both trials is likely to have affected the results of superiority and noninferiority, as both were assessed using the ITT population. It is likely that the impact was small, as the results were consistent on noninferiority between the ITT and PP populations, given that results on PP population are more conservative for the inference on noninferiority.

Across both trials, the most common protocol violation was that the patient's visit fell outside the visit window. This occurred for 26.9% of patients in APOLLO and 24.0% of patients in LUNAR, and occurred more frequently in the timolol maleate 0.5% arms. Background noise attributed to factors including protocol violations (e.g., use of drugs effecting IOP and discontinuation due to AE) could lead to a bias in favour of the study drug, particularly under the noninferiority design.

The large number of patients with protocol violations may have resulted in violation of the constancy assumption. The constancy assumption requires that the effect of the active comparator in the noninferiority trial is consistent with the effect observed in previous trials. This is particularly important with previous trials of timolol compared with placebo, which were conducted several years ago under different patient population and clinical settings.

External Validity

In APOLLO and LUNAR, patients were recruited from a number of countries, with 84.8% and 96.9% of patients recruited from the US, respectively. Despite none of the patients being recruited from Canada, the clinical expert consulted in this review suggested that the study population was generally representative of Canadian adult patients seen in clinical practice.

The study populations in APOLLO and LUNAR consisted of patients who were 18 years of age and older; thus, the data are not generalizable to the pediatric population.

The mean baseline IOP of the study population in both trials was approximately 26 mm Hg to 27 mm Hg, which represents a moderately elevated IOP considering that many patients

have progressive glaucoma at lower IOPs. Patients were also required to have an IOP less than or equal to 36 mm Hg at all three measurement time points in both eyes; therefore, the treatment benefit-and-risk profile among patients with IOPs less than 26 mm Hg or greater than 36 mm Hg remains unknown. These criteria produce a population that is likely more restrictive than the population that may actually be treated in clinic, which reduces the generalizability of the results. Across both trials, patients were excluded if they had a history or current presence of a number of disorders, including but not limited to: severe dysfunction of the liver or the kidneys, wasting disease, angina pectoris not controlled by medical or surgical treatment, or severe asthma.

The population included in the trials was mixed, with some being treatment-naive and others being treatment-experienced. This mixed population does not necessarily reflect real-world practice in Canada. The majority of the study population were treatment-experienced in both trials; thus, the benefit-and-risk profile observed may not be generalizable to treatment-naive patients. The most common first-line therapy is with PGAs due to favourable effectiveness, once-daily administration, and tolerability compared with the other drugs, including beta-blockers.[2,17,18] For this reason, the choice of timolol maleate 0.5% as the comparator was not ideal. It can be argued that, given the information provided by multiple agencies, including the Canadian Ophthalmological Society, a PGA would be a more relevant comparator.

While APOLLO and LUNAR included subgroup data based on treatment-naive versus treatment-experienced patients, subgroup data were not available based on baseline disease severity or baseline IOP.

The three-month study treatment periods were sufficient for observing treatment differences in the primary end point and the two key secondary end points in both LUNAR and APOLLO. The current review includes open-label safety extension trials of nine-month and three-month durations for APOLLO and LUNAR, respectively (Appendix 6). These safety extensions are based on all patients continuing or switching to treatment with LBN 0.024% ophthalmic solution for the duration of the trial. The results of these safety extensions indicate no notable differences in mean IOP at different time points, nor in mean diurnal IOP between treatment groups. In comparison with the efficacy phases of the two trials, no new or cumulative safety concerns emerged from the APOLLO and LUNAR extension studies. The extension studies for APOLLO and LUNAR were limited by the uncontrolled and unblinded nature of the safety phases. While the duration of the safety extensions was likely sufficient to observe harms associated with LBN 0.024% ophthalmic solution, the durations of the efficacy phases of the trials were too short to observe the long-term effects of LBN 0.024% ophthalmic solution on IOP and visual acuity compared with relevant comparators.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Table 9. See Appendix 4 for detailed efficacy data.

Intraocular Pressure

Mean Intraocular Pressure

In both APOLLO and LUNAR, the LS mean IOP in patients' study eyes was numerically lower in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5%

arm at all nine time points (8:00 a.m., 12:00 p.m., and 4:00 p.m. at week 2, week 6, and month 3) (Table 9). In APOLLO, the difference between trial arms was statistically significant across all nine time points. In LUNAR, the difference between trial arms was statistically significant across eight out of nine time points, with the first time point (week 2 at 8:00 a.m.) showing a difference that was not statistically significant.

In APOLLO, the treatment difference between arms ranged from −1.03 mm Hg (95% CI, −0.37 mm Hg to −1.68 mm Hg) to −1.37 mm Hg (95% CI, −0.69 mm Hg to −2.05 mm Hg). In LUNAR, the treatment difference between arms ranged from −0.44 mm Hg (95% CI, 0.26 mm Hg to −1.13 mm Hg) to −1.34 mm Hg (95% CI, −0.72 mm Hg to −1.95 mm Hg).

Noninferiority was determined in both APOLLO and LUNAR, as the upper limit of the CIs did not exceed 1.5 mm Hg at any of the nine time points and did not exceed 1.0 mm Hg for at least five out of the nine time points. In APOLLO, the criteria for superiority of LBN 0.024% ophthalmic solution compared with timolol maleate 0.5% was met, as the upper limit of the 95% CI did not exceed 0 mm Hg at any of the nine time points. In LUNAR, the criteria for superiority were not met due to the treatment difference at the first time point (week 2 at 8:00 a.m.).

In APOLLO, results for the outcome of LS mean change on IOP were consistent with results based on the PP population (Appendix 4) and sensitivity analyses using WOCF and MI techniques to impute missing data. In LUNAR, some differences were observed for the results of the PP population. For this population, the difference between trial arms was not statistically significant at the 5% level of significance at any of the nine time points; however, the criteria for noninferiority were still met. The sensitivity analyses in LUNAR using WOCF and MI techniques to impute missing data showed results that were consistent with the main analysis. In both APOLLO and LUNAR, subgroup analyses revealed no difference based on prior treatment status (treatment-experienced compared with treatment-naive).

In the open-label safety extension phases of APOLLO and LUNAR, no notable differences were observed for LS mean IOP between treatment arms (Appendix 6).

Intraocular Pressure Less Than or Equal to 18 mm Hg

In both APOLLO and LUNAR, the proportion of patients with IOP less than or equal to 18 mm Hg at all nine time points was numerically greater in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm in the first three months (Table 9). In APOLLO and LUNAR, respectively, 22.0% and 17.7% of patients in the LBN 0.024% ophthalmic solution arms had IOP of less than or equal to 18 mm Hg at all nine time points, versus 11.3% and 11.1% of patients in the timolol maleate 0.5% arms. The difference of proportions was statically significant in APOLLO (11.6%; 95% CI, 4.3% to 18.9%; $P = 0.005$) but not in LUNAR (6.6%; 95% CI, −0.4 to 13.5; $P = 0.084$).

In both APOLLO and LUNAR, results for this outcome were consistent with results based on the PP population in each trial. In APOLLO, subgroup analysis revealed differences based on prior treatment status, with treatment-experienced patients showing results in favour of LBN 0.024% ophthalmic solution over timolol maleate 0.5% (Appendix 5). In LUNAR, no difference was found based on prior treatment status (treatment-experienced compared with treatment-naive).

Intraocular Pressure Reduction Greater Than or Equal to 25%

In both APOLLO and LUNAR, the proportion of patients with IOP reduction greater than or equal to 25% at all nine time points was numerically greater in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm in the first three months (Table 9).

In APOLLO and LUNAR, respectively, 34.9% and 31.0% of patients in the LBN 0.024% ophthalmic solution arm had IOP reduction greater than or equal to 25% at all nine time points, versus 19.5% and 18.5% in the timolol maleate 0.5% arms. The difference in proportions was statically significant in both APOLLO (15.3%; 95% CI, 6.6% to 24.0%; *P* = 0.001) and LUNAR (12.5%; 95% CI, 4.0% to 21.1%; *P* = 0.007).

The results for this outcome were consistent with the results based on the PP population in APOLLO, but not in LUNAR (difference in proportion = 9.5; 95% CI, –0.9% to 19.9%). In both APOLLO and LUNAR, subgroup analyses revealed differences based on prior treatment status, with treatment-experienced patients showing results in favour of LBN 0.024% ophthalmic solution over timolol maleate 0.5% (Appendix 5).

Visual Acuity

BCVA was assessed at baseline and month 3 in both APOLLO and LUNAR, and remained similar between arms at both time points in both trials (Table 9). In APOLLO, the mean BCVA was 0.09 LogMAR (SD = 0.137) for the LBN 0.024% ophthalmic solution arm and 0.07 LogMAR (SD = 0.124) for the timolol maleate 0.5% arm at baseline. At month 3, the mean BCVA remained consistent at 0.08 LogMAR (SD = 0.134) for the LBN 0.024% ophthalmic solution arm and 0.07 LogMAR (SD = 0.139) for the timolol maleate 0.5% arm. In LUNAR, the mean BCVA was 0.09 LogMAR (SD = 0.135) for the LBN 0.024% ophthalmic solution arm and 0.07 LogMAR(SD = 0.119) for the timolol maleate 0.5% arm at baseline. At month 3, the mean BCVA remained consistent at 0.08 LogMAR (SD = 0.121) for the LBN 0.024% ophthalmic solution arm and 0.07 LogMAR (SD = 0.133) for the timolol maleate 0.5% arm. Statistical analysis was not performed on this outcome.

[redacted]

Optic Nerve

[redacted]

[redacted]

Table 9: Key Efficacy Outcomes

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% N = 135
IOP				
Baseline – diurnal				
Mean, mm Hg[a] (range)	26.73 (24.0 to 35.7)	26.49 (24.0 to 36.0)	26.61 (24.0 to 35.0)	26.43 (24.0 to 33.5)
Week 2 at 8:00 a.m.				
Mean (mm Hg)[b]	18.61	19.84	19.17	19.61
Treatment difference[c], adjusted mean[d] (95% CI)[e]	–1.22 (–0.54 to –1.91)		−0.44 (0.26 to −1.13)	
P value[d]	< 0.001		0.216	
Week 2 at 12:00 p.m.				
Mean (mm Hg)[b]	18.00	19.37	18.46	19.22
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.37 (–0.69 to –2.05)		−0.76 (−0.11 to −1.42)	
P value[d]	< 0.001		0.022	
Week 2 at 4:00 p.m.				
Mean (mm Hg)[b]	18.09	19.20	18.10	18.79
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.11 (–0.46 to –1.76)		−0.69 (−0.09 to −1.29)	
P value[d]	< 0.001		0.025	
Week 2 – diurnal				
Mean (mm Hg)[b]	18.24	19.51	18.59	19.22
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.28 (–1.88 to –0.68)		−0.63 (−1.21 to −0.05)	
Week 2 – diurnal CFB				
Mean, mm Hg[a] (range)	–8.45 (–16.7 to 0.7)	–7.06 (–17.7 to 2.0)	–8.00 (–20.3 to 6.3)	–7.27 (–14.3 to 3.0)
Week 6 at 8:00 a.m.				
Mean (mm Hg)[b]	18.59	19.63	18.67	19.59
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.04 (–0.38 to –1.70)		−0.92 (−0.28 to −1.56)	
P value[d]	0.002		0.005	
Week 6 at 12:00 p.m.				
Mean (mm Hg)[b]	17.84	19.09	18.02	18.86
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.25 (–0.62 to –1.88)		−0.84 (−0.23 to −1.45)	
P value[d]	< 0.001		0.007	
Week 6 at 4:00 p.m.				
Mean (mm Hg)[b]	17.82	19.09	17.87	18.85

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% N = 135
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.27 (–0.58 to –1.96)		−0.98 (−0.35 to −1.61)	
P value[d]	< 0.001		0.003	
Week 6 – diurnal				
Mean (mm Hg)[b]	18.10	19.32	18.21	19.10
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.21 (–1.81 to –0.62)		−0.90 (−1.46 to −0.33)	
Week 6 – diurnal CFB				
Mean, mm Hg[a] (range)	–8.59 (–17.8 to 3.8)	–7.25 (–15.5 to 0.3)	–8.38 (–17.5 to 6.3)	–7.38 (–15.7 to 4.7)
Month 3 at 8:00 a.m.				
Mean (mm Hg)[b]	18.71	19.73	18.68	19.56
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.03 (–0.37 to –1.68)		−0.88 (−0.25 to −1.51)	
P value[d]	0.002		0.006	
Month 3 at 12:00 p.m.				
Mean (mm Hg)[b]	17.88	19.15	17.92	19.21
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.27 (–0.61 to –1.92)		−1.29 (−0.67 to −1.91)	
P value[d]	< 0.001		< 0.001	
Month 3 at 4:00 p.m.				
Mean (mm Hg)[b]	17.83	19.15	17.72	19.06
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.32 (–0.64 to –2.01)		−1.34 (−0.72 to −1.95)	
P value[d]	< 0.001		< 0.001	
Month 3 – diurnal				
Mean (mm Hg)[b]	18.16	19.40	18.13	19.28
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.24 (–1.84 to –0.64)		−1.15 (−1.71 to −0.58)	
Month 3 – diurnal CFB				
Mean, mm Hg[a] (range)	–9.07 (–19.0 to 4.0)	–7.17 (–16.3 to 1.7)	−8.46 (–19.3 to 6.3)	–7.20 (–17.8 to 1.0)
Mean IOP ≤ 18 mm Hg at All 9 Efficacy-Phase Time Points				
N (%)	65 (22.9)	15 (11.3)	49 (17.7)	15 (11.1)
Difference of proportions[f] (95% CI)	11.6 (4.3 to 18.9)		6.6 (−0.4 to 13.5)	
P value[g]	0.005		0.084	
Per Cent Reduction From Baseline in Mean IOP ≥ 25% at All 9 Efficacy-Phase Time Points[h]				
N (%)	99 (34.9)	26 (19.5)	86 (31.0)	25 (18.5)
Difference of proportions[f] (95% CI)	15.3 (6.6 to 24.0)		12.5 (4.0 to 21.1)	
P value[g]	0.001		0.007	
BCVA in the Study Eye[i] (LogMAR)				
Baseline				

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% N = 135
N	283	135	277	135
Mean (SD)	0.09 (0.137)	0.07 (0.124)	0.09 (0.135)	0.07 (0.119)
Month 3				
N	270	127	261	130
Mean (SD)	0.08 (0.134)	0.07 (0.139)	0.08 (0.121)	0.07 (0.133)
Optic Nerve[i]				
Baseline				
Normal	249 (88.0)	119 (88.1)	224 (80.9)	104 (77.0)
Abnormal	34 (12.0)	16 (11.9)	53 (19.1)	31 (23.0)
Month 3				
Normal	239 (87.9)	113 (89.0)	211 (80.8)	100 (76.9)
Abnormal	30 (11.0)	14 (11.0)	49 (18.8)	29 (22.3)
Not done	3 (1.1)	0	1 (0.4)	1 (0.8)
Missing	11	8	16	5
New abnormalities on Month 3[j]	1 (0.4)	1 (0.8)	0	0

BCVA = best-corrected visual acuity; CFB = change from baseline; CI = confidence interval; IOP = intraocular pressure; LBN = latanoprostene bunod; LogMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

[a] Derived mean IOP assessment value or derived mean diurnal IOP assessment value, respectively.

[b] Mean was the least squares mean of the mean IOP for the corresponding time point and visit at time-matched overall average baseline under ANCOVA.

[c] Treatment difference = LBN 0.024% ophthalmic solution – timolol maleate 0.5%.

[d] Adjusted mean, 95% CIs, and *P* values were from an ANCOVA model with treatment as a classification variable and time-matched baseline mean IOP as a covariate.

[e] Noninferiority was to be claimed if the upper limit of the CIs < 1.5 mm Hg at all time points of each visit and < 1.0 mm Hg for at least 5 out of the 9 time points in the efficacy phase. If noninferiority was determined, superiority at each time point was to be claimed if the upper limit of the 95% CI < 0 mm Hg at all time points of each visit in the efficacy phase.

[f] Difference = LBN 0.024% ophthalmic solution – timolol maleate 0.5%.

[g] The *P* values were from Pearson's chi-square test.

[h] Per cent reduction from baseline = 100 × (baseline mean IOP – post-baseline mean IOP) ÷ baseline mean IOP.

[i] Safety population based on actual treatment group (the treatment received the most during the efficacy phase).

[j] New abnormalities are any month 3 abnormalities that were assessed as normal or missing at baseline.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Harms

Table 10 contains detailed data on harms that occurred during the three-month efficacy phase. Harms data related to the open-label, single-arm extension trials are described in Appendix 6.

Adverse Events

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[redacted]

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Serious Adverse Events

[redacted]

Withdrawals Due to Adverse Events

[redacted]

Mortality

[redacted]

Notable Harms

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Table 10: Harms

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Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Discussion

Summary of Available Evidence

APOLLO and LUNAR were three-month pivotal trials included in the review. They were multi-centre, double-masked, parallel-group, noninferiority, active-controlled, and manufacturer-sponsored. Patients in APOLLO and LUNAR were randomized in a 2:1 ratio for treatment with LBN 0.024% ophthalmic solution (once daily in the evening) and vehicle (once daily in the morning) or timolol maleate 0.5% twice daily. LBN 0.024% ophthalmic solution is believed to use a novel mechanism of action that is likely to act by increasing the outflow of aqueous humour through both uveoscleral and trabecular meshwork.

APOLLO and LUNAR included patients who were 18 years of age and older with a diagnosis of OAG or OHT in one or both eyes. After washout, patients were required to have a mean or median IOP greater than or equal to 26 mm Hg at a minimum of one time point, greater than or equal to 24 mm Hg at a minimum of one time point, and greater than or equal to 22 mm Hg at one time point in the same eye. Patients were also required to have an IOP less than or equal to 36 mm Hg at all three measurement time points in both eyes. Patients were excluded if they had a history or current presence of a number of disorders including but not limited to: severe dysfunction of the liver or the kidneys, wasting disease, angina pectoris not controlled by medical or surgical treatment, or severe asthma.

APOLLO and LUNAR evaluated several outcomes relating to IOP. Based on the primary efficacy outcome of mean IOP in patients' study eye at nine time points, noninferiority was determined in both trials. Superiority for treatment with LBN 0.024% ophthalmic solution compared with timolol maleate 0.5% was determined for APOLLO but not LUNAR. In both APOLLO and LUNAR, the proportion of patients with IOP less than or equal to 18 mm Hg was numerically greater in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm; however, significant differences were found in APOLLO only. In both APOLLO and LUNAR, the proportion of patients with IOP reduction greater than or equal to 25% was numerically greater and statistically significant in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm. Other relevant outcomes, including HRQoL and VRQoL, were not assessed; this highlights a major limitation to the trials.

Additional evidence for open-label safety extensions for APOLLO and LUNAR — and for JUPITER, a Japanese, single-arm, open-label study — is summarized and appraised in Appendix 6. A manufacturer-supplied indirect treatment comparison (ITC) comparing LBN 0.024% ophthalmic solution to relevant comparators is summarized in Appendix 7.

Interpretation of Results

Efficacy

The two individual trials, APOLLO and LUNAR, were very similar in terms of study design and study populations as per the baseline characteristics. Given these similarities, the reason for the differences in the key primary and one of the key secondary outcomes between the trials is unclear.

IOP was assessed extensively in both trials (e.g., mean IOP at each time point, patients with IOP less than or equal to 18 mm Hg, patients with IOP reduction greater than or equal

to 25%) and was determined to be an appropriate surrogate outcome, since visual field loss and vision loss would take several years to manifest, according to the clinical expert consulted for this review.[11]

While the focus on IOP reduction seen in these trials was relevant and consistent with the literature, several other outcomes identified by patients were not assessed as efficacy outcomes. Visual acuity and appearance of the optic nerve were considered as safety outcomes in the trials and were not assessed statistically. APOLLO and LUNAR were limited with respect to the assessment of patient-reported outcomes. Outcomes related to HRQoL and VRQoL were identified as important to patients, but were not assessed in either of the trials. There is insufficient evidence to support a correlation between glaucoma treatment and patient-reported outcomes.[11] The absence of patient-reported outcomes introduces uncertainty with respect to the clinical relevance of the results. Outcomes related to visual field loss and glaucoma symptoms were not assessed in either of the trials.

The 1.5 mm Hg noninferiority margin was selected based on discussion with the FDA on historical glaucoma noninferiority studies as well as on historical data from landmark glaucoma trials. However, no minimal clinically important differences (MCIDs) for IOP were identified in the published literature. The use of 1.5 mm Hg as the noninferiority margin may not have been clinically meaningful given that IOP levels typically fluctuate between 2 mm Hg and 5 mm Hg.[2] The proportion of patients who reached the normal range (defined as less than 18 mm Hg in IOP after 3 months) was higher for the LBN 0.024% ophthalmic solution arms than the timolol maleate 0.5% arms, with treatment differences of 11.6% (APOLLO) and 6.6% (LUNAR). The difference in the proportion of patients with IOP reduction greater than or equal to 25% at all nine time points was greater in the LBN 0.024% ophthalmic solution arms than in the timolol maleate 0.5% arms (15.3% in APOLLO, 12.5% in LUNAR). The improvements related to treatment with LBN 0.024% ophthalmic solution indicate modest clinical relevance, according to the clinical expert consulted for this review.

Visual acuity (assessed through BCVA) and the appearance of the optic nerve remained similar between arms at both baseline and month 3 in both trials.

Overall, LBN 0.024% ophthalmic solution appeared to be better than timolol maleate 0.5%, with unknown or perhaps only modest clinical implications.

Open-label safety extension trials of nine months' and three months' duration for APOLLO and LUNAR, respectively, assessed patients who either continued on or switched to treatment with LBN 0.024% ophthalmic solution (Appendix 6). The results of these safety extensions indicate no notable differences in mean IOP at different time points, nor in mean diurnal IOP between treatment groups. Additionally, results pertaining to visual acuity and the appearance of the optic nerve were similar to the results observed in the efficacy phase at month 3 (Appendix 6). These open-label safety extensions were limited by the uncontrolled and unblinded nature of the safety phases. While the durations of the safety extensions were likely sufficient to observe harms associated with LBN 0.024% ophthalmic solution, the durations of the efficacy phases of the trials were too short to observe the long-term effects of LBN 0.024% ophthalmic solution on IOP and visual acuity compared with relevant comparators.

An open-label, uncontrolled, single-arm, Japanese study (JUPITER) was designed to assess the long-term safety and efficacy of LBN 0.024% ophthalmic solution once daily in one or both eyes of patients with OAG or OHT (Appendix 6). The results of this trial

revealed a mean IOP in week 52 (n = 121) of 14.42 mm Hg, with a statistically significant reduction of IOP from baseline of 5.25 mm Hg. While these findings showed favourable results for the use of LBN 0.024% ophthalmic solution, the study remains descriptive in nature due to the lack of a comparator arm and its uncontrolled, open-label nature. In addition, the results from this study cannot necessarily be generalized to patients of other races due to anatomical differences in the eyelids of Japanese patients, who often have increased IOP measurements during the manual manipulation needed to perform GAT.

The choice for using timolol maleate 0.5% as the active comparator presents a major limitation to the study design as it is based on information inconsistent with current guidance from multiple agencies, including the Canadian Ophthalmological Society, the American Academy of Ophthalmology, and NICE. These agencies acknowledge that in the past, beta-blockers were considered first-line therapy; however, they state that currently, PGAs are the most common first-line therapy due to favourable effectiveness, once-daily administration, and tolerability compared with other drugs, including beta-blockers.[2,17,18] Based on this evidence, timolol maleate 0.5% was not the most relevant comparator with respect to applicability to the Canadian population. Using a beta-blocker that is not a currently accepted first-line therapy increases the likelihood of noninferiority and superiority for LBN 0.024% ophthalmic solution. It can be argued that a PGA would have been a more relevant comparator, given the information provided by the agencies. Direct evidence from a 29-day dose-finding phase II trial (VOYAGER) compared various concentrations of LBN ophthalmologic solutions with the PGA latanoprost 0.005% ophthalmic solution and found statistically significantly lower mean study-eye diurnal IOPs for LBN ophthalmologic solution 0.024%.[32] VOYAGER's conclusion was not supported by the results of the manufacturer-provided ITC of phase III trials.

The results of the ITC indicate that treatment with LBN 0.024% ophthalmic solution is likely favourable over placebo; however, little can be elucidated about its efficacy compared with other products. Overall, the results of this analysis must be interpreted with caution because their utility and robustness are limited by issues with transparency in the systematic review methods and analysis as well as by the absence of control for heterogeneity.

Harms

In APOLLO and LUNAR, the most common ocular AEs (in the study eye) were related to conjunctival hyperemia and eye irritation. In APOLLO, serious adverse events (SAEs) occurred in 1.1% and 1.5% of patients in the LBN 0.024% ophthalmic solution arm and timolol maleate 0.5% arm, respectively. In LUNAR, SAEs occurred in 2.2% and 0% of patients in the LBN 0.024% ophthalmic solution arm and timolol maleate 0.5% arm, respectively. Withdrawals due to adverse events (WDAEs) similarly occurred across treatment arms in both trials, with the most common WDAEs related to eye disorders.

The product monograph notes the potential for ophthalmologic harms related to bacterial keratitis, eyelash changes, intraocular inflammation, macular edema, and pigmentation. The occurrence of these AEs was not of note in APOLLO and LUNAR.

Across trials, ocular AEs (in the study eye) occurred more frequently in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm. In LUNAR, differences in ocular AEs specifically relating to conjunctival hyperemia and eye irritation show a marked increase for patients treated with LBN 0.024% ophthalmic solution compared with timolol maleate 0.5%. While there is also an increase seen in APOLLO,

it is numerically much smaller than that observed in LUNAR. Given the similar design of the efficacy phases and the similarity in baseline characteristics between the two trials, it is unclear why this substantial difference in ocular AEs exists for LUNAR but not for APOLLO. In comparison with the efficacy phases of APOLLO and LUNAR, no new or cumulative safety concerns emerged from the open-label extension studies. In these safety extensions, the most common ocular treatment-emergent adverse events reported were eye irritation, eye pain, and conjunctival hyperemia. During the LUNAR study, in both the efficacy and safety phases, the percentage of patients reporting conjunctival hyperemia (in the study eye and in the treated fellow eye) was higher in the LBN 0.024% arm than in the timolol maleate 0.5% crossover to LBN 0.024% arm. A similar difference was not apparent in the APOLLO trial. In both phases of the LUNAR trial, patients in the LBN 0.024% treatment arm experienced a higher incidence of ocular disorders. During the LUNAR safety phase, the number of new patients with ocular AEs in the timolol maleate 0.5% crossover to LBN 0.024% arm appeared to offset the difference observed between the two treatment arms in the efficacy phase. This pattern was not observed in APOLLO. No notable pattern of SAEs was observed in the APOLLO and LUNAR extension studies.

Overall, the safety profiles in terms of eye-related complications favoured timolol maleate 0.5% versus LBN 0.024% ophthalmic solution. The manufacturer-supplied ITC did not perform analysis on harms-related outcomes.

Potential Place in Therapy[2]

Glaucoma is the leading cause of irreversible blindness globally[12-14] and is estimated to affect 2.7% of Canadians aged 40 years and older.[5] The term glaucoma includes a group of diseases that are broadly classified as open- or closed-angle. Currently, the only proven treatment for all types of glaucoma is lowering IOP,[11] which can be done with medication, laser, or surgery.[15] The initial management of glaucoma is usually medical, with eye drops. There are currently five classes of medications to manage glaucoma: prostaglandin analogues, beta-blockers, carbonic anhydrase inhibitors, alpha2 adrenergic agonists, and miotics. Some patients are not able to achieve sufficient IOP lowering (often termed target pressure) with the current available medication (due either to lack of efficacy or tolerance) and progress to interventions such as laser or surgery.[16]

Latanoprostene bunod 0.024% (Vyzulta) represents a new class of IOP-lowering medication. In addition to acting as a prostaglandin analogue, LBN is expected to release nitric oxide, which in turn is expected to reduce IOP by relaxing the trabecular meshwork and Schlemm's canal to improve outflow. This represents a new mechanism of action that may facilitate IOP lowering in patients who are unable to achieve their target pressure with currently available glaucoma hypotensive medications.

Since all glaucomas are treated by lowering IOP, Vyzulta could potentially be of benefit for both open- and closed-angle glaucomas. The first-line medical therapies for glaucoma, barring any contraindications, are the prostaglandin analogues. This medication class is very effective in lowering eye pressure. The medications are easy to use (given that they are used only once a day) and well tolerated. The Ontario Drug Benefit program requires a limited-use form for many glaucoma medications, including the prostaglandin analogues. The limited-use code is to confirm that either the patient was unsuccessful with a beta-blocker or that a beta-blocker is contraindicated.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Despite this requirement, prostaglandin analogues are usually initiated before a beta-blocker due to the reasons cited previously. However, many patients cannot be controlled with one class of medication; for these patients, adjunctive hypotensive drops are prescribed. The second hypotensive drop is usually a beta-blocker. Additional hypotensive drops are added if a target pressure is not achieved, whether due to lack of response, insufficient eye pressure reduction, or intolerance. Maximal medical therapy is usually three or four classes of medication. If a patient has not reached their target pressure but is not on three or four classes of medication, either due to intolerance or nonresponse, then Vyzulta should be considered, as it is a new class of hypotensive drop. Vyzulta would be considered a single drug with two mechanisms of action and would replace a prostaglandin. Some ophthalmologists may also consider using Vyzulta as a first-line therapy; however, the high rate of hyperemia may limit its widespread us as a first-line drug.

Conclusions

APOLLO and LUNAR were three-month, randomized, double-blind, active-controlled trials that met the inclusion criteria for this review. In both trials, noninferiority (assessed using mean IOP at nine time points) was achieved for treatment with once-daily LBN 0.024% ophthalmic solution compared with twice-daily timolol maleate 0.5%.

Overall, LBN 0.024% ophthalmic solution appeared to be better than timolol maleate 0.5%, with unknown or perhaps only modest clinical implications, whereas the safety profiles in terms of eye-related complications favour timolol maleate 0.5%. Outcomes related to HRQoL and VRQoL were identified as important to patients, but were not assessed in either of the trials.

[redacted]

Ocular AEs occurred more frequently in the LBN 0.024% ophthalmic solution arm compared with the timolol maleate 0.5% arm in both trials. In LUNAR specifically, differences in ocular AEs relating to conjunctival hyperemia and eye irritation showed a marked increase for those treated with LBN 0.024% ophthalmic solution compared with timolol maleate 0.5%. While there was also an increase seen in APOLLO, it was numerically much smaller than what was observed in LUNAR.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

Three different patient organizations worked together to submit one patient input for this submission. These included the Canadian Council of the Blind (CCB), the Canadian National Institute for the Blind (CNIB), and the Foundation Fighting Blindness (FFB).

The CCB is a registered charity whose purpose is to provide people with vision loss a distinctive and unique perspective before governments. Using peer support and various recreational and social activities, the CCB encourages active living and rehabilitation among people affected by vision loss.

The CNIB is an organization that aims to create an inclusive, accessible, and barrier-free society for people affected by impaired sight by providing them with the necessary tools and rehabilitation therapy to live safe, fulfilling, and independent lives.

The FFB is a charitable funding organization whose mission is to lead the fight against blindness by advancing retinal disease research, education, and public awareness.

No funding has been received by the CCB, the CNIB, or the FFB from Bausch Health, Canada Inc. in the past two years, and none of these organizations had any conflicts of interest to declare with regard to this submission.

2. Condition-Related Information

The FFB posted and disseminated an online, 30-question burden-of-illness survey on July 20, 2018 in response to the call for patient experiences for the minimally invasive glaucoma surgery (MIGS) Health Technology Assessment. This survey aimed to ascertain patients' collective perspectives about the various aspects and burdens associated with glaucoma.

Glaucoma is a disease of the optic nerve that can lead to ever-increasing visual impairment and ultimately blindness in some patients. The severity of glaucoma varies significantly in those affected, with patients ranging between experiencing no vision loss to complete blindness. Responses to the survey underscored the importance of how many patients simply misinterpreted their disease as a symptom of normal aging, so did not follow up with their physicians prior to there being more progressed and irreversible damage to their optic nerves. This misconception that the disease is "normal" or "inevitable" thus remains problematic.

Patients in the survey described their glaucoma as ranging from "very serious" to "not at all serious." While the psychological, physical, and financial burdens of the disease ranges among patients, all domains can be profoundly affected as the severity of visual impairment increases over time. Psychologically, patients experience everything from anxiety to depression. They are faced with a constant reminder of their disease due to ever-increasing limitations and the fact that they have to put multiple eye drops into their eyes, sometimes several times a day. In addition, the constant fear of impending blindness can paralyze a patient with a sense of powerlessness, leading them into a spiral of fear associated with a worsening condition.

The physical challenges and loss of independence associated with sight impairment cannot be overstated. While the effects on daily living vary with the degree of visual impairment, patients noted difficulties with the ability to function independently. General mobility, cooking, sewing, vacuuming, and other household chores, walking through public areas, driving, travelling, gardening, and being physically active are some of the challenges that patients face. Some patients are no longer being able to enjoy things they did prior to their diagnosis. In addition, the ability to read, write, and ensure that things are clean (e.g., dishes, floors) are all affected to varying degrees. These issues further affect patients' psychological well-being and independence.

Patients with glaucoma also face many barriers. The cost of medication, transportation to and from specialist appointments, and the length of time to reach these specialists can be problematic. In addition, the constant need for eye drops or the time and recovery associated with other treatment paradigms (primarily surgical) can present as barriers. Accommodations must also sometimes be made (such as increasing the size of television or computer monitors), thus adding other barriers that often need to be overcome.

While not specifically mentioned in the survey responses, the associated loss of independence undoubtedly affects spouses and other caregivers as they would be required to aid the patient with daily activities and take them to appointments. The time potentially lost to employment and the interference with their independent activities should not be understated.

3. Current Therapy-Related Information

The majority of surveyed patients had experience with drug therapy in the form of eye drops or pills, while others did not take any medication. Some patients received laser eye surgery, conventional surgery, or MIGS. The majority of surveyed patients had also never been made aware of other treatments or medication options or alternatives to the treatments they were currently receiving.

Most surveyed patients were comfortable with the idea of drug therapy (in the form of eye drops or pills), while a lesser proportion were okay with receiving laser surgery, conventional surgery, or MIGS. In terms of disease management, many patients noted the burden associated with daily, multiple administrations of eye drops and the increased potential for issues with adherence.

4. Expectations About the Drug Being Reviewed

This combined submission focused on a survey relating to the CADTH MIGS Health Technology Assessment, which did not include specific questions regarding Vyzulta; however, it was evident that patients are always open to new to additional treatment options.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) Embase (1974 to present) Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 20, 2018
Alerts:	Weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
/	At the end of a phrase, searches the phrase as a subject heading

MULTI-DATABASE STRATEGY	
1.	(vyzulta* or vesneo* or latanoprostene or BOL-303259* or BOL303259* or NCX-116 or NCX116 or PF-3187207 or PF3187207 or I6393O0922).ti,ab,kf,ot,hw,rn,nm.
2.	1 use medall
3.	*latanoprostene/
4.	(vyzulta* or latanoprostene or vesneo* or BOL-303259* or BOL303259* or NCX-116 or NCX116 or PF-3187207 or PF3187207).ti,ab,kw,dq.
5.	or/3-4
6.	5 use oemezd
7.	6 not conference abstract.pt.

MULTI-DATABASE STRATEGY
8. 2 or 7
9. remove duplicates from 8

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- Studies for Vyzulta, latanoprostene OR BOL-303259-X]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.

Grey Literature

Dates for Search:	December 17-18, 2018
Keywords:	Vyzulta/latanoprostene/BOL-303259
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- Internet search
- open access journals.

Appendix 3: Excluded Studies

Table 11: Excluded Studies

Reference	Reason for Exclusion
Liu JHK, Slight JR, Vittitow JL, Scassellati Sforzolini B, Weinreb RN. Efficacy of Latanoprostene Bunod 0.024% Compared With Timolol 0.5% in Lowering Intraocular Pressure Over 24 Hours. Am J Ophthalmol. 2016;169:249-257.[33]	Phase II trial
Weinreb RN, Liebmann JM, Martin KR, Kaufman PL, Vittitow JL. Latanoprostene Bunod 0.024% in Subjects With Open-angle Glaucoma or Ocular Hypertension: Pooled Phase 3 Study Findings. J Glaucoma. 2018;27(1):7-15.[34]	Pooled findings
Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. Br J Ophthalmol. 2015;99(6):738-745.[35]	Phase II trial
Hoy SM. Latanoprostene Bunod Ophthalmic Solution 0.024%: A Review in Open-Angle Glaucoma and Ocular Hypertension.[Erratum appears in Drugs. 2018 Jun;78(8):857; PMID: 29846910]. Drugs. 2018;78(7):773-780.[36]	Study design (review)

Appendix 4: Detailed Outcome Data

Table 12: Intraocular Pressure Efficacy Outcomes by Treatment Status for APOLLO and LUNAR

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% N = 135
IOP[a]				
Week 2 at 8:00 a.m.				
Mean (mm Hg)	18.64	19.87	19.32	19.78
Difference (95% CI)	–1.23 (–1.91 to –0.54)		−0.47 (−1.16 to 0.22)	
Treatment status interaction *P* value	0.272		0.497	
Week 2 at 12:00 p.m.				
Mean (mm Hg)	17.99	19.36	18.53	19.31
Difference (95% CI)	–1.37 (–2.05 to –0.69)		−0.78 (−1.43 to −0.13)	
Treatment status interaction *P* value	0.251		0.706	
Week 2 at 4:00 p.m.				
Mean (mm Hg)	18.16	19.28	18.16	18.86
Difference (95% CI)	–1.12 (–1.77 to –0.47)		−0.70 (−1.30 to −0.10)	
Treatment status interaction *P* value	0.488		0.914	
Week 6 at 8:00 a.m.				
Mean (mm Hg)	18.62	19.67	18.77	19.71
Difference (95% CI)	–1.05 (–1.71 to –0.38)		−0.94 (−1.58 to −0.30)	
Treatment status interaction *P* value	0.186		0.642	
Week 6 at 12:00 p.m.				
Mean (mm Hg)	17.89	19.15	18.06	18.91
Difference (95% CI)	–1.26 (–1.88 to –0.63)		−0.85 (−1.46 to −0.24)	
Treatment status interaction *P* value	0.220		0.416	
Week 6 at 4:00 p.m.				
Mean (mm Hg)	17.87	19.15	17.89	18.88
Difference (95% CI)	–1.28 (–1.97 to –0.59)		−0.98 (−1.62 to −0.35)	
Treatment status interaction *P* value	0.913		0.783	
Month 3 at 8:00 a.m.				
Mean (mm Hg)	18.70	19.73	18.72	19.61
Difference (95% CI)	–1.03 (–1.68 to –0.37)		−0.89 (−1.52 to −0.26)	

	APOLLO		LUNAR	
Treatment status interaction *P* value	0.439		0.050	
Month 3 at 12:00 p.m.				
Mean (mm Hg)	17.82	19.07	17.90	19.18
Difference (95% CI)	–1.26 (–1.91 to –0.60)		−1.28 (−1.90 to −0.66)	
Interaction *P* value	0.057		0.366	
Month 3 at 4:00 p.m.				
Mean (mm Hg)	17.80	19.12	17.77	19.13
Difference (95% CI)	–1.32 (–2.01 to –0.63)		−1.35 (−1.97 to −0.74)	
Treatment status interaction *P* value	0.279		0.689	
Mean IOP ≤ 18 mm Hg at All 9 Efficacy-Phase Time Points				
Treated				
N (%)	47/201 (23.4)	11/99 (11.1)	35/195 (17.9)	12/101 (11.9)
Difference of proportions[b] (95% CI)	12.3 (3.8 to 20.8)		6.1 (−2.2 to 14.4)	
Untreated				
N (%)	18/83 (21.7)	4/34 (11.8)	14/82 (17.1)	3/34 (8.8)
Difference of proportions[b] (95% CI)	9.9 (–4.1 to 23.9)		8.2 (−4.3 to 20.8)	
Per Cent Reduction From Baseline in Mean IOP ≥ 25% at All 9 Efficacy-Phase Time Points[c]				
Treated				
N (%)	70/201 (34.8)	18/99 (18.2)	63/195 (32.3)	18/101 (17.8)
Difference of proportions[b] (95% CI)	16.6 (6.6 to 26.7)		14.5 (4.5 to 24.4)	
Untreated				
N (%)	29/83 (34.9)	8/34 (23.5)	23/82 (28.0)	7/34 (20.6)
Difference of proportions[b] (95% CI)	11.4 (–6.2 to 29.0)		7.5 (−9.3 to 24.2)	

ANCOVA = analysis of covariance; CI = confidence interval; IOP = intraocular pressure; LBN = latanoprostene bunod.

Note: The initial ANCOVA model included terms for time-matched baseline mean IOP, treatment status, randomized treatment, and randomized treatment-by-treatment-status interaction. The reduced ANCOVA model included terms for time-matched baseline mean IOP, treatment status, and randomized treatment.

[a] If the *P* value of the interaction term from the initial model was < 0.05 for a given visit and time point combination, the main effects and randomized treatment comparison for that visit and time point combination are not applicable and do not appear; otherwise, the remainder of the results for that visit and time point combination are from the reduced model.

[b] Difference = LBN 0.024% ophthalmic solution – timolol maleate 0.5%.

[c] Per cent reduction from baseline = 100 × (baseline mean IOP – post-baseline mean IOP) ÷ baseline mean IOP.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Table 13: Key Efficacy Outcomes (Per-Protocol Analysis Set)

	APOLLO		LUNAR	
	LBN 0.024% N = 192	Timolol Maleate 0.5% N = 80	LBN 0.024% N =183	Timolol Maleate 0.5% N = 87
Week 2 at 8:00 a.m.				
Mean (mm Hg)[a]	18.60	19.67	19.08	19.26
Treatment difference,[b] adjusted mean[c] (95% CI)	–1.07 (–0.26 to –1.87)		–0.18 (0.66 to –1.02)	
P value[c]	0.010		0.677	
Week 2 at 12:00 p.m.				
Mean (mm Hg)[a]	17.92	19.14	18.47	18.99
Treatment difference,[b] adjusted mean[c] (95% CI)	–1.22 (–0.42 to –2.02)		–0.52 (0.31 to –1.35)	
P value[c]	0.003		0.221	
Week 2 at 4:00 p.m.				
Mean (mm Hg)[a]	17.84	19.29	18.17	18.58
Treatment difference,[b] adjusted mean[c] (95% CI)	–1.45 (–0.68 to –2.22)		–0.41 (0.31 to –1.12)	
P value[c]	< 0.001		0.261	
Week 6 at 8:00 a.m.				
Mean (mm Hg)[a]	18.55	19.58	18.53	18.94
Treatment difference,[b] adjusted mean[c] (95% CI)	–1.03 (–0.25 to –1.81)		–0.41 (0.32 to –1.14)	
P value[c]	0.010		0.268	
Week 6 at 12:00 p.m.				
Mean (mm Hg)[a]	17.63	19.10	18.00	18.70
Treatment difference,[b] adjusted mean[c] (95% CI)	–1.47 (–0.74 to –2.19)		–0.69 (0.08 to –1.47)	
P value[c]	< 0.001		0.080	
Week 6 at 4:00 p.m.				
Mean (mm Hg)[a]	17.53	19.02	17.88	18.61
Treatment difference,[b] adjusted mean[c] (95% CI)	–1.49 (–0.68 to –2.31)		–0.73 (0.04 to –1.51)	
P value[c]	< 0.001		0.065	
Month 3 at 8:00 a.m.				
Mean (mm Hg)[a]	18.39	19.69	18.65	19.03
Treatment difference,[b] adjusted mean[c] (95% CI)	–1.31 (–0.55 to –2.06)		–0.38 (0.35 to –1.10)	
P value[c]	< 0.001		0.308	
Month 3 at 12:00 p.m.				
Mean (mm Hg)[a]	17.61	19.17	18.05	18.72
Treatment difference,[b] adjusted mean[c] (95% CI)	–1.56 (–0.82 to –2.29)		–0.67 (0.12 to –1.46)	
P value[c]	< 0.001		0.097	
Month 3 at 4:00 p.m.				
Mean (mm Hg)[b]	17.48	19.16	17.89	18.66

	APOLLO		LUNAR	
Treatment difference,[c] adjusted mean[d] (95% CI)[e]	–1.67 (–0.88 to –2.46)		–0.77 (–0.00 to –1.54)	
P value[d]	< 0.001		0.050	
Mean IOP ≤ 18 mm Hg at All 9 Efficacy-Phase Time Points				
N (%)	44 (22.9)	6 (7.5)	32 (17.5)	11 (12.6)
Difference of proportions[f] (95% CI)	15.4 (7.1 to 23.7)		4.8 (–4.0 to 13.7)	
P value[g]	0.003		0.310	
Per Cent Reduction From Baseline in Mean IOP ≥ 25% at All 9 Efficacy-Phase Time Points[h]				
N (%)	68 (35.4)	15 (18.8)	51 (27.9)	16 (18.4)
Difference of proportions[f] (95% CI)	16.7 (5.8 to 27.6)		9.5 (–0.9 to 19.9)	
P value[g]	0.007		0.092	

ANCOVA = analysis of covariance; BCVA = best-corrected visual acuity; CI= confidence interval; IOP = intraocular pressure; LBN = latanoprostene bunod.

[a] Derived mean IOP assessment value or derived mean diurnal IOP assessment value, respectively.

[b] Mean was the least squares mean of the mean IOP for the corresponding time point and visit at time-matched overall average baseline under ANCOVA.

[c] Treatment difference = LBN 0.024% ophthalmic solution – timolol maleate 0.5%.

[d] Adjusted mean, 95% CIs, and *P* values were from an ANCOVA model with treatment as a classification variable and time-matched baseline mean IOP as a covariate.

[e] Noninferiority was to be claimed if the upper limit of the CIs was < 1.5 mm Hg at all time points of each visit and < 1.00 mm Hg for at least 5 out of the 9 time points in the efficacy phase. If noninferiority was determined, superiority at each time point was to be claimed if the upper limit of the 95% CI was < 0 mm Hg at all time points of each visit in the efficacy phase.

[f] Difference = LBN 0.024% ophthalmic solution – timolol maleate 0.5%.

[g] The *P* values were from Pearson's chi-square test.

[h] Per cent reduction from baseline = 100 × (baseline mean IOP – post-baseline mean IOP) ÷ baseline mean IOP.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Goldmann applanation tonometry (GAT)
- intraocular pressure (IOP).

Table 14: Validity and Minimal Clinically Important Differences of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
GAT	A clinical technique to measure IOP by determining the force needed to flatten a certain area of the cornea.	Yes; however, there are known limitations using GAT.	N/A	Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee 2009,[2] Sudesh 1993,[31] Dielemans 1994,[30] Wachtl, 2017[29]
IOP	Measured through tonometry procedures, IOP is an outcome that guides the diagnosis, treatment, and prognosis of increased intraocular pressure and open-angle glaucoma. Potential prognostic quantification is based on changes in IOP.	N/A	Unknown	Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee, 2009[2]

IOP = intraocular pressure; GAT = Goldmann applanation tonometry; MCID = minimal clinically important difference; N/A = not applicable.

Findings

Goldmann Applanation Tonometry

GAT is identified as the gold standard in measuring IOP[29] and is recommended for such by the Canadian Ophthalmological Society glaucoma guidelines and the National Institute for Health and Care Excellence (NICE) glaucoma guidelines.[2,13,30,31]

The reliability of IOP measurement using GAT has been established.[30,31] In a study conducted by Dielemans et al.,[30] 62 patients (mean age, 69.6 years) with and without glaucoma were enrolled to measure inter- and intra-observer variation in IOP measurements in both eyes. Two observers measured the IOP three consecutive times, with 10 minutes between each measurement. The investigators calculated the median IOP, standard deviation (SD), and coefficient of variation for each set of three measurements. Mean difference in the median IOP measurements as well as the correlation between the median IOP readings between the two investigators were used to report on the inter-observer variation. The mean difference of the first IOP reading compared with subsequent readings was used as a measure of intra-observer reliability. Also, the mean difference between the first IOP reading and the other two was compared between the two observers as a measure of inter-observer reliability. The results reported in the study show a 1.60 mm Hg (SD 2.15) mean difference in median IOP measurements between observers. The reported correlation coefficient between observers was 0.87 for the left eye and 0.75 for the right eye. The mean difference in median IOP within observers was 1.50 mm Hg (SD 1.96). The mean difference between first IOP readings from each set of three was 1.79 mm Hg

(SD 2.41) between observers and 1.64 (SD 2.07) within observers. The authors reported that using the median of three IOP readings reduced the variability of the reading by about 10%. The authors concluded that a median of three measurements may be more reliable than a single reading, as this approach reduced the variability of the reading by about 10%. However, the clinical importance of this decrease in variability is unclear.[30]

The second study, conducted by Sudesh et al., examined accuracy and variability in IOP measurement using GAT.[31] This study enrolled 16 patients and eight tonometrists (observers), who were randomly assigned to receive GAT training or no training. An observer conducted four consecutive IOP readings on one eye, followed by four consecutive readings from another observer on the same eye. Subsequently, the second observer conducted four IOP readings on the other eye, followed by four readings from the first observer. The study reported the mean IOP reading in trained versus untrained tonometrists and the mean IOP readings from each individual tonometrist. The authors reported that the difference in mean IOP reading in trained versus untrained tonometrists was 1.12 mm Hg (standard error 0.44). The first set of four readings had a higher mean IOP than the second set of readings (difference, 0.71 mm Hg, standard error, 0.19 mm Hg). The authors also compared the mean IOP from four readings between observers. They reported that the difference in mean IOP was ≥ 2 mm Hg for 26% of observers and ≥ 3 mm Hg for 19% of observers.[31]

These two studies suggest that GAT produces reliable IOP readings;[30,31] however, there is evidence that GAT accuracy is somewhat limited.[29] These limitations are mainly due to variations in measurements of central corneal thickness; these can vary considerably. Goldmann calibrated his tonometer based on the assumption that 500 µm was a normal reading; however, there is a tendency for GAT to overestimate IOP on thicker corneas and underestimate it on thin corneas.[29] The underestimation is more concerning (as it is clinically acceptable to have a slight overestimation), given that this may lead to delayed glaucoma diagnoses and a subsequent delay in essential treatment.[29] Wachtl et al.[29] performed a cross-sectional case series on 112 adult patients with glaucoma, testing IOP using GAT (both corrected and uncorrected readings) and Pascal dynamic contour tonometry (DCT) measurements. The goal was to assess the degree of discordance between the two measures as well as between the state of glaucoma and discordant IOP measurements. When compared with DCT measurements (DCT measures IOP continuously and directly while eliminating the errors associated with corneal thickness), GAT measurements were more discordant in patients with advanced glaucoma and thin corneas, even when using GAT-based correction formulas. Therefore, the authors advise caution when assessing IOP with GAT-based measurements.[29]

Variability in IOP measurements is around 1 mm Hg to 2 mm Hg, as indicated by the available evidence, and depends on the observer and timing of measurement.

Intraocular Pressure

The validity and reliability of IOP measurement depends on the tool used to make the IOP readings. No minimal clinically important difference (MCID) was identified in the published literature. Instead, the Canadian Ophthalmic Society recommends assigning an IOP upper threshold as a goal of therapy based on the severity of glaucoma as follows:[2]

- Patient for whom a clinical decision is made to treat: 24 mm Hg, with at least 20% reduction from baseline
- Early: 20 mm Hg, with at least 25% reduction from baseline

- Moderate: 17 mm Hg, with at least 30% reduction from baseline
- Advanced: 14 mm Hg, with at least 30% reduction from baseline[2]

The suggested upper limit of the target IOP should be modified based on a patient's long life, quality of life, and risk factors for progression.[2]

Correlation of Intraocular Pressure Lowering with Clinical Outcomes

A 2013 systematic review produced by the United States Preventive Services Task Force assessed the result of medical treatment on visual field loss and optic nerve damage in open-angle glaucoma (OAG).[37] The authors reported three systematic reviews and 21 randomized controlled trials (RCTs) that fit the inclusion criteria of the review. The authors indicated that there was high-quality evidence that lowering IOP reduces the risk of optic nerve damage and visual field loss. However, there was insufficient evidence relating to the effect of glaucoma treatment on patient-reported outcomes (i.e., quality of life, activity limitation, patient-reported visual loss).[37]

The effect of treating ocular hypertension (OHT) and OAG compared with no treatment was evaluated in a 2005 systematic review and meta-analysis.[11] The study included a meta-analysis of five RCTs of patients with OHT. The results indicated that IOP reduction decreased the rate of progression to glaucoma compared with no treatment (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.39 to 0.81). In addition, the meta-analyzed result of two of the included RCTs indicated that treating glaucoma reduced the rate of progression of visual field loss compared with no treatment (HR, 0.65; 95% CI, 0.49 to 0.87). No formal quality assessment was performed in this systematic review.[11]

Conclusion

Several professional bodies, including the Canadian Ophthalmological Society, consider GAT as the gold standard to measure IOP. Evidence suggests that GAT provides reliable measurements, although there are known limitations associated with its use, mainly based on corneal thickness. However, there is a potential variation of 1 mm Hg to 2 mm Hg with measurement, which may depend on the GAT operator and time of measurement. A systematic review and meta-analysis of five RCTs of patients with OHT and OAG found that reducing IOP decreased the rate of progression to glaucoma compared with no treatment.

Appendix 6: Summary of Other Studies (Open-label Extension for APOLLO and LUNAR, and JUPITER)

APOLLO and LUNAR Extension Studies

Aim

To summarize the details and findings of two open-label extension studies:

- APOLLO (Study #769; NCT01749904)[7]
- LUNAR (Study #770; NCT01749930).[8]

Findings

Study Design

The APOLLO and LUNAR safety extensions are multi-centre, prospective, open-label, uncontrolled crossover studies of the phase III double-blind (DB) randomized controlled trial (RCT) studies 769 and 770, for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) in one or both eyes.[7,8]

The APOLLO safety phase was designed to assess the long-term safety and efficacy of up to 12 months of treatment with latanoprostene bunod (LBN) 0.024% ophthalmic solution once daily; the LUNAR study, with the same objectives, sustained LBN treatment for up to six months. Patients in either study who completed the three-month efficacy phase with no major protocol deviations, without occurrence of a relevant exclusion criterion, and with no adverse events (AEs) of unacceptable risk were eligible to rollover into their respective extension studies (safety phase), in which all patients were treated with LBN 0.024% once daily.[7,8]

In both studies, patients randomized to the timolol maleate 0.5% arm of the efficacy phase were crossed over to LBN 0.024% after the three-month (visit 6) data collection time point. Study eligibility criteria were similar during the efficacy and safety phases with an exception. Upon entering the safety phase, if a patient had a diagnosis of OAG or OHT in both eyes, regardless of eligibility as per IOP criteria during the efficacy phase, both eyes were treated. Assessments were made at three-month intervals: at six, nine, and 12 months after the start date (day 1) in the APOLLO study and six months after the start date in the LUNAR study.[7,8]

Population Demographics and Baseline Disease Characteristics

Population demographics and baseline disease characteristics for the efficacy phases (DB RCT) and safety phases (open-label extension) are summarized in the main body of the clinical review report (Table 5).

Intervention

During the safety extensions, all patients were instructed to instill one drop of LBN 0.024% ophthalmic solution in the affected eye(s) once daily in the evening at approximately

8:00 p.m. Patients randomized to the LBN 0.024% arm during the efficacy phase could receive a total of 12 months of LBN 0.024% exposure (APOLLO study) or six months of exposure (LUNAR study). Patients randomized to the timolol maleate 0.5% crossover to LBN 0.024% ophthalmic solution arm could receive a maximum nine-month treatment with LBN 0.024% ophthalmic solution in the APOLLO study or a maximum three-month treatment in the LUNAR study.[7,8]

Outcomes

The primary purpose of the APOLLO extension study was to monitor the safety of LBN 0.024% ophthalmic solution once daily over a treatment course of up to 12 months, while the LUNAR study monitored patients for up to six months. The reported outcomes for the APOLLO and LUNAR extension trials included:

- In the study eyes of all patients, at each visit (three-month intervals): mean IOP (diurnal as well as at three time points [8:00 a.m., 12:00 p.m., and 4:00 p.m.]).
- Safety assessments: monitoring and reporting of AEs; best-corrected visual acuity (BCVA) results and ophthalmoscopy findings for the optic nerve in both eyes.

Means presented in the safety phase are absolute, and are not adjusted by analysis of covariance (ANCOVA). In the extension trial data, IOP means are presented for the study eye only; BCVA and optic nerve measurements are provided for both eyes.[7,8]

Patient Disposition and Exposure

Patient disposition for the efficacy phase (DB RCT) and safety phase (open-label extension) is reported in the main body of the clinical review report (Table 6). The number and proportion of intention-to-treat (ITT) patients completing both the APOLLO efficacy and safety phases was, respectively, 250/284 (88.0%) in the LBN 0.024% ophthalmic solution arm and 110/133 (82.7%) in the timolol maleate 0.5% with crossover to LBN 0.024% ophthalmic solution arm. In LUNAR, 253/278 (91.0%) for the LBN 0.024% arm and 125/136 (91.9%) for the crossover arm completed both phases.[7,8]

The safety population for the entire APOLLO study was considered 418 (with 283 patients in the LBN 0.024% arm and 135 patients in the timolol maleate 0.5% crossover to LBN 0.024% arm), among whom 406 patients were exposed to at least one dose of LBN 0.024% (283 and 123, respectively). The LUNAR study had a safety population of 415 patients, with 279 patients in the LBN 0.024% arm and 136 patients in the timolol maleate 0.5% crossover to LBN 0.024% arm, among whom 406 were exposed to at least one dose of LBN 0.024% (279 and 127, respectively). Exposure to LBN 0.024% is summarized in Table 14.[7,8]

[redacted]

[redacted]

Table 15: Summary of Exposure to Latanoprostene Bunod 0.024% Ophthalmic Solution (Safety Population)

[redacted]

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Efficacy

Efficacy outcomes in the APOLLO and LUNAR extension studies for IOP in the study eye, as well as BCVA and optic nerve measurements in the study eye and the treated fellow eye, are presented in Table 16. IOP outcomes were obtained from the ITT population; BCVA and optic nerve assessments were obtained from the safety population.

Intraocular Pressure

In the APOLLO extension trial, the mean IOP at each visit (month 6, 9, and 12) for the three time points (8:00 a.m., 12:00 p.m., and 4:00 p.m.) ranged from 18.75 mm Hg to 17.58 mm Hg (in the LBN 0.024% arm) compared with 18.71 mm Hg to 17.08 mm Hg (in the timolol maleate 0.5% crossover to LBN 0.024% arm). The diurnal means reported for the LBN 0.024% arm at month 6, 9, and 12, respectively, were: 17.96 mm Hg (n = 261), 18.19 mm Hg (n = 254), and 17.89 mm Hg (n = 250). At month 6, 9, and 12, in the crossover arm, the diurnal means were: 18.04 mm Hg (n = 121), 17.62 mm Hg (n = 111), and 17.58 mm Hg (n = 110), respectively.[7]

In the LUNAR extension trial, the mean IOPs at month 6 for the three time points (8:00 a.m., 12:00 p.m., and 4:00 p.m., respectively) were: 18.56 mm Hg, 17.91 mm Hg,

and 17.95 mm Hg (LBN 0.024% arm) compared with 18.41 mm Hg, 17.60 mm Hg, and 17.59 mm Hg (timolol maleate 0.5% crossover to LBN 0.024% arm). The diurnal means reported at month 6 for the two treatment arms were 18.14 mm Hg (n = 257) and 17.93 mm Hg (n = 127), respectively.[8]

In the timolol maleate 0.5% crossover to LBN 0.024% arm, in both studies, the comparison between month 3 IOP values in the efficacy phases and the subsequent IOP values in the safety phases may suggest a decrease in mean IOP upon treatment with LBN 0.024%.[7,8]

Data were not presented for the proportion of patients with IOP less than or equal to 18 mm Hg, nor for the proportion of patients with an IOP reduction greater than or equal to 25%.

Visual Acuity

[redacted]

Optic Nerve

[redacted]

[redacted]

Table 16: Efficacy Outcomes in Safety Phases

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 135
IOP[A]				
Month 6 at 8:00 a.m.				
n	261	120	257	127
Mean[b] (SD) in mm Hg	18.49 (3.340)	18.71 (4.071)	18.56 (2.974)	18.41 (3.514)
Month 6 at 12:00 p.m.				
n	261	119	257	126

	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 135
Mean[b] (SD) in mm Hg	17.74 (3.283)	17.80 (4.315)	17.91 (3.053)	17.6 (2.863)
Month 6 at 4:00 p.m.				
n	260	120	256	126
Mean[b] (SD) in mm Hg	17.64 (3.328)	17.48 (3.923)	17.95 (3.168)	17.59 (2.868)
Month 6 – diurnal				
n	261	121	257	127
Mean[b] (SD) in mm Hg	17.96 (2.994)	18.04 (3.888)	18.14 (2.751)	17.93 (3.005)
Month 9 at 8:00 a.m.				
n	254	111	NA	NA
Mean[b] (SD) in mm Hg	18.75 (3.713)	18.33 (3.255)	NA	NA
Month 9 at 12:00 p.m.				
n	253	111	NA	NA
Mean[b] (SD) in mm Hg	17.87 (3.296)	17.41 (2.878)	NA	NA
Month 9 at 4:00 p.m.				
n	253	111	NA	NA
Mean[b] (SD) in mm Hg	17.90 (3.580)	17.12 (2.820)	NA	NA
Month 9 – diurnal				
n	254	111	NA	NA
Mean[b] (SD) in mm Hg	18.19 (3.276)	17.62 (2.676)	NA	NA
Month 12 at 8:00 a.m.				
n	250	110	NA	NA
Mean[b] (SD) in mm Hg	18.32 (3.420)	18.19 (2.916)	NA	NA
Month 12 at 12:00 p.m.				
n	250	110	NA	NA
Mean[b] (SD) in mm Hg	17.76 (3.441)	17.47 (2.757)	NA	NA
Month 12 at 4:00 p.m.				
n	250	110	NA	NA
Mean[b] (SD) in mm Hg	17.58 (3.110)	17.08 (2.801)	NA	NA
Month 12 – diurnal				
n	250	110	NA	NA
Mean[b] (SD) in mm Hg	17.89 (3.042)	17.58 (2.565)	NA	NA
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	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 135
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	APOLLO		LUNAR	
	LBN 0.024% N = 284	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 133	LBN 0.024% N = 277	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 135
[redacted]				

BCVA = best-corrected visual acuity; CSR = clinical study report; IOP = intraocular pressure; ITT = intention to treat; LBN = latanoprostene bunod; SD = standard deviation.

[a] IOP results are for study eye only (ITT population).

[b] Means: derived equals derived mean IOP assessment value or derived mean diurnal IOP assessment value, respectively. For a given patient, visit, time point, and eye, the derived mean IOP was the mean of two consecutive measurements. If these measurements differed by more than 2 mm Hg, a third measurement was taken, and the derived mean IOP was the median of the three measurements. If the third measurement was indicated, but not done, the derived mean IOP was the higher-measured IOP if post-baseline, or the lower-measured IOP if at baseline. For a given patient, visit, and eye, derived mean diurnal IOP was the mean of the respective non-missing derived mean IOPs (8:00 a.m., 12:00 p.m., 4:00 p.m.).

[c] Safety population.

[d] New abnormalities are any abnormalities in month 3 that were assessed as normal or missing at baseline.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Harms

Harm outcomes from the APOLLO and LUNAR complete trials (both phases combined) are presented in Table 17. Generally, in both studies, the treatment-emergent adverse events (TEAEs) were considered to be mild to moderate in severity. The percentage of patients experiencing at least one non-ocular TEAE was similar between the two treatment arms in APOLLO (23.3% and 21.5% in the LBN 0.024% and the timolol maleate 0.5% crossover to LBN 0.024% arms, respectively) and in LUNAR (16.1% and 17.6%, respectively). The majority was considered not related to the study drug by the investigator.[7,8]

In APOLLO, the percentage of patients reporting ocular TEAEs was similar between treatment arms (LBN 0.024%, and timolol maleate 0.5% crossover to LBN 0.024%) in both the study eye (20.1% and 20.7%, respectively) and the fellow eye (21.0% and 22.4%, respectively).[7]

Similarly, in the LUNAR study, the percentage of patients with ocular AEs was comparable between treatment arms (LBN 0.024%, and timolol maleate 0.5% crossover to LBN 0.024%) in both the study eye (28.2% and 26.7%, respectively) and the fellow eye (28.5% and 26.1%, respectively). However, the percentages of ocular TEAEs in LUNAR were slightly higher than those reported in the APOLLO study. Furthermore, during the LUNAR efficacy phase, treatment with LBN 0.024% (in study and treated fellow eyes) was associated with an approximately 10% higher incidence of ocular TEAEs compared with the timolol maleate 0.5% arm. This 10% difference was reduced during the safety phase when patients treated with timolol maleate 0.5% crossed over to LBN 0.024% treatment. This trend was not observed in the APOLLO study.[7,8]

In both APOLLO and LUNAR, the most common ocular TEAEs fell under the standard of care of eye disorders. Among treatment arms and treated eyes (study eye and treated fellow eye), the percentage of patients experiencing eye disorders ranged from 18.4% to 20.1% (APOLLO) and from 25.2% to 26.7% (LUNAR). The majority of TEAEs were considered related to the study drug by the study investigator. Only one TEAE occurred at a frequency greater than 10%: conjunctival hyperemia, which was notably higher in both eyes among patients in the LUNAR LBN 0.024% treatment arm than in patients in the other study arms.[7,8]

Among ocular TEAEs, the most commonly reported TEAEs for the study eye in the LBN 0.024% arm and the timolol maleate 0.5% crossover to LBN 0.024% arm, respectively, were:

- conjunctival hyperemia (APOLLO: 3.5% and 3.0%; LUNAR: 11.6% and 3.7%)
- eye irritation (APOLLO: 5.7% and 2.2%; LUNAR: 7.6% and 9.6%)
- eye pain (APOLLO: 2.1% and 3.0%; LUNAR: 6.1% and 5.9%).

The most commonly reported ocular TEAEs for the treated fellow eye, in the LBN 0.024% arm and the timolol maleate 0.5% crossover to LBN 0.024% arm, respectively, were:

- conjunctival hyperemia (APOLLO: 4.7% and 3.7%; LUNAR: 11.9% and 3.7%)
- eye irritation (APOLLO: 4.7% and 2.2%; LUNAR: 7.4% and 9.0%)
- eye pain (APOLLO: 2.5% and 1.5%; LUNAR: 7.0% and 6.0%).

During the APOLLO safety phase, severe ocular TEAEs reported in the study eye of patients in the LBN 0.024% arm included blepharospasm, allergic conjunctivitis, increased IOP, and an eyelid tumour. Only the incidence of allergic conjunctivitis was considered probably related to the study drug by the investigator. Two severe ocular TEAEs were reported in the treated fellow eye of one patient in the LBN 0.024% arm: allergic conjunctivitis and increased IOP. Only the allergic conjunctivitis was considered probably related to the study drug by the investigator. Patients in the timolol maleate 0.5% crossover to LBN 0.024% arm did not report any severe TEAEs in the safety phase of APOLLO.[7]

During the LUNAR extension study, severe ocular TEAEs reported in the study eye of patients in the LBN 0.024% arm included severe conjunctival hyperemia and severe retinal vein occlusion requiring surgical intervention. Neither was considered probably related to the study drug by the investigator. One patient in the LBN 0.024% arm experienced severe conjunctival hyperemia in the treated fellow eye, considered possibly related to the study drug by the investigator. All other ocular TEAEs were mild to moderate in severity. Patients

in the timolol maleate 0.5% crossover to LBN 0.024% arm did not report any severe TEAEs in the safety phase of LUNAR.[8]

[redacted]

One death occurred during the LUNAR study. The patient was randomized to the LBN 0.024% arm and completed the efficacy phase. Approximately one month after entering the safety phase of the study, the patient died of severe ischemic heart disease, confirmed by autopsy. The patient had a previous medical condition of coronary artery disease.[8]

Table 17: Harms – Total Study Duration for Safety Population

	APOLLO		LUNAR	
	LBN 0.024% N = 283	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 135	LBN 0.024% N = 279	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 136
TEAEs[a]				
Non-Ocular AEs				
N	**283**	**135**	**279**	**136**
Patients with > 0 AE, n (%)	66 (23.3)	29 (21.5)	45 (16.1)	24 (17.6)
Most common AEs[a]				
Gastrointestinal disorders	9 (3.2)	2 (1.5)	6 (2.2)	2 (1.5)
Infections and infestations	34 (12.0)	16 (11.9)	14 (5.0)	10 (7.4)
Bronchitis	5 (1.8)	1 (0.7)	4 (1.4)	2 (1.5)
Cystitis	0	2 (1.5)		
Nasopharyngitis	5 (1.8)	3 (2.2)	3 (1.1)	3 (2.2)
Upper respiratory tract infection	2 (0.7)	2 (1.5)	2 (0.7)	2 (1.5)
Injury, poisoning, and procedural complications	10 (3.5)	8 (5.9)	6 (2.2)	2 (1.5)
Fall	3 (1.1)	3 (2.2)	3 (1.1)	1 (0.7)

	APOLLO		LUNAR	
	LBN 0.024% N = 283	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 135	LBN 0.024% N = 279	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 136
Metabolism and nutrition Disorders	4 (1.4)	2 (1.5)	3 (1.1)	0
Musculoskeletal and connective tissue disorders	10 (3.5)	6 (4.4)	8 (2.9)	4 (2.9)
Pain in extremity	1 (0.4)	0	3 (1.1)	1 (0.7)
Rotator cuff syndrome	1 (0.4)	2 (1.5)		
Nervous system disorders	6 (2.1)	4 (3.0)	8 (2.9)	5 (3.7)
Headache	2 (0.7)	1 (0.7)	3 (1.1)	3 (2.2)
Psychiatric disorders	1 (0.4)	2 (1.5)	3 (1.1)	1 (0.7)
Respiratory, thoracic, and mediastinal disorders	7 (2.5)	1 (0.7)	4 (1.4)	6 (4.4)
Cough	2 (0.7)	0	0	2 (1.5)
Rhinorrhea	0	1 (0.7)	0	2 (1.5)
Vascular disorders	3 (1.1)	1 (0.7)	4 (1.4)	2 (1.5)
Hypertension	3 (1.1)	1 (0.7)	3 (1.1)	2 (1.5)
Ocular AEs (Study Eye)				
N	**283**	**135**	**277**	**135**
Patients with > 0 AE, n (%)	57 (20.1)	28 (20.7)	78 (28.2)	36 (26.7)
Eye disorders	52 (18.4)	26 (19.3)	73 (26.4)	34 (25.2)
Conjunctival hyperaemia	10 (3.5)	4 (3.0)	32 (11.6)	5 (3.7)
Dry eye	4 (1.4)	1 (0.7)	4 (1.4)	1 (0.7)
Eye irritation	16 (5.7)	3 (2.2)	21 (7.6)	13 (9.6)
Eye pain	6 (2.1)	4 (3.0)	17 (6.1)	8 (5.9)
Foreign body sensation in eyes	4 (1.4)	1 (0.7)	3 (1.1)	1 (0.7)
Ocular hyperemia	4 (1.4)	3 (2.2)	8 (2.9)	3 (2.2)
Vision blurred	0	1 (0.7)	5 (1.8)	4 (3.0)
Eye pruritis	1 (0.4)	1 (0.7)	4 (1.4)	4 (3.0)
Asthenopia	NA	NA	1 (0.4)	2 (1.5)
Punctate keratitis	1 (0.4)	4 (3.0)	4 (1.4)	1 (0.7)
General disorders and administration site conditions	6 (2.1)	2 (1.5)	7 (2.5)	1 (0.7)
Instillation site pain	4 (1.4)	2 (1.5)	4 (1.4)	1 (0.7)
Skin and subcutaneous tissue disorders	2 (0.7)	0	3 (1.1)	0
Ocular AEs (Treated Fellow eye)				
N	**276**	**134**	**270**	**134**
Patients with > 0 AE, n (%)	58 (21.0)	30 (22.4)	77 (28.5)	35 (26.1)
Eye disorders	55 (19.9)	27 (20.1)	72 (26.7)	34 (25.4)
Conjunctival hyperaemia	13 (4.7)	5 (3.7)	32 (11.9)	5 (3.7)
Eye irritation	13 (4.7)	3 (2.2)	20 (7.4)	12 (9.0)
Eye pain	7 (2.5)	2 (1.5)	19 (7.0)	8 (6.0)

	APOLLO		LUNAR	
	LBN 0.024% N = 283	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 135	LBN 0.024% N = 279	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 136
Foreign body sensation in eyes	6 (2.2)	1 (0.7)	3 (1.1)	1 (0.7)
Ocular hyperemia	3 (1.1)	3 (2.2)	7 (2.6)	3 (2.2)
Eye pruritis	1 (0.4)	2 (1.5)	5 (1.9)	4 (3.0)
Dry eye	5 (1.8)	1 (0.7)	5 (1.9)	0
Vision blurred	1 (0.4)	1 (0.7)	4 (1.5)	4 (3.0)
Punctate keratitis	2 (0.7)	3 (2.2)	4 (1.5)	1 (0.7)
General disorders and administration site conditions	5 (1.8)	4 (3.0)	6 (2.2)	2 (1.5)
Instillation site pain	4 (1.5)	3 (2.2)	5 (1.9)	1 (0.7)
Skin and subcutaneous tissue disorders	2 (0.7)	0	3 (1.1)	0
SAEs				
Patients with > 0 SAEs, n (%)	7 (2.5)	9 (6.7)	7 (2.5)	0
Most common reasons (SOC)				
Nervous system disorders	2 (0.7)	1 (0.7)	0	NA
Immune system disorder	0	2 (1.5)	0	NA
Cardiac disorder	0	0	2 (0.7)	NA
Injury, poisoning, or procedural complication	1 (0.4)	1 (0.7)	2 (0.7)	NA
WDAEs				
WDAEs, n (%)	7 (2.5)	9 (6.7)	5 (1.8)	4 (3.0)
Most common reasons				
Eye disorders	3 (1.1)	4 (3.0)	2 (0.7)	2 (1.5)
Investigations (increased or elevated IOP)	1 (0.4)	3 (2.2)	0	0
Deaths				
Number of deaths, n (%)	0	0	1 (0.4)	0
Notable Harms				
Study Eye				
Macular edema	1 (0.4)	0	0	0
Iris hyperpigmentation	1 (0.4)	0	0	0
Conjunctival hyperemia	10 (3.5)	4 (3.0)	32 (11.6)	5 (3.7)
Eye irritation	16 (5.7)	3 (2.2)	21 (7.6)	13 (9.6)
Eye pain	6 (2.1)	4 (3.0)	17 (6.1)	8 (5.9)
Eye dryness	4 (1.4)	1 (0.7)	4 (1.4)	1 (0.7)
Skin pigmentation disorder/ hyperpigmentation	1 (0.4)	0	2 (0.7)	0
Treated Fellow Eye				
Macular edema	0	0	0	0
Iris hyperpigmentation	1 (0.4)	0	0	0
Conjunctival hyperemia	13 (4.7)	5 (3.7)	32 (11.9)	5 (3.7)

	APOLLO		LUNAR	
	LBN 0.024% N = 283	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 135	LBN 0.024% N = 279	Timolol Maleate 0.5% Crossover to LBN 0.024% N = 136
Eye irritation	13 (4.7)	3 (2.2)	20 (7.4)	12 (9.0)
Eye pain	7 (2.5)	2 (1.5)	19 (7.0)	8 (6.0)
Eye dryness	5 (1.8)	1 (0.7)	5 (1.9)	0
Skin pigmentation disorder/ hyperpigmentation	1 (0.4)	0	2 (0.7)	0

AE = adverse event; LBN = latanoprostene bunod; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in category; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Notes: Adverse events are coded with MedDRA version 13.0. Patients with more than one occurrence of SOC/PT in the study eye were counted only once for that SOC/PT with regard to TEAEs in the study eye, as defined in footnote "a." Patients with more than one occurrence of SOC/PT in the treated fellow eye were counted only once for that SOC/PT with regard to TEAEs in the treated fellow eye as defined in footnote "a." One patient was randomized to LBN 0.024% ophthalmic solution, but used timolol maleate in the efficacy phase.

[a] Data are reported for the safety population throughout the entire study length (efficacy and safety phases). TEAEs were all AEs known to start or worsen following the first administration of study drug and on or before the day of the last dose of the study drug +30 days.

Source: Clinical Study Reports for APOLLO[7] and LUNAR.[8]

Limitations

The uncontrolled nature of the extension studies and the bias of attrition rates for later time points are key limitations when assessing the safety and efficacy of LBN 0.024% ophthalmic solution in the long term.

Analyses for clinically and statistically meaningful differences were not possible for the APOLLO and LUNAR extension studies. Both were open-label crossover studies in which all patients were treated with LBN 0.024% ophthalmic solution. As all patients in these safety phases received the same treatment, the interpretation of the results was mostly restricted to descriptive and non-statistical comparative assessments. Thus, the study design is unable to definitively measure the extent to which the treatment effects observed in the DB RCT efficacy phases were maintained.

In the APOLLO efficacy phase, the percentages of discontinuations in the LBN 0.024% and the timolol maleate 0.05% arms were 7.0% and 7.5%, respectively; while throughout the entire study, the percentages of discontinuations were 12.0% and 17.3%, respectively. The LUNAR study reported withdrawals in the efficacy phase at 6.8% and 5.9% in the LBN 0.024% and the timolol maleate 0.05% arms, respectively; these rates were 9.0% and 8.1%, respectively, throughout the entire study. In both extension studies, for each subsequent time point, fewer patients contributed to the data set, potentially skewing the results. The population lost to a long-term extension study may enrich the apparent success of the study, as those who remain are more likely those achieving study goals and tolerating treatment, compared with those who discontinue the treatment and/or the study altogether.[7,8]

Both extension studies were unblinded, which can introduce bias in the reporting of outcomes and AEs and in the analysis of data. The APOLLO and LUNAR safety findings for once-daily LBN 0.024% ophthalmic solution are limited to the length of the clinical trial treatments (up to 12 months or six months, respectively) and may not inform long-term treatment outcomes.

Summary

The APOLLO and LUNAR extension studies were open-label, uncontrolled crossover safety phases designed to assess the long-term safety and efficacy of once-daily LBN 0.024% ophthalmic solution for the treatment of OAG or OHT in one or both eyes. Patients could receive up to 12 months or nine months (APOLLO), or six or three months (LUNAR) of once-daily LBN 0.024%, depending on their randomization assignment in the efficacy phase. The mean extent of exposure to LBN 0.024% ranged from 337.5 days (APOLLO) to 175.8 days (LUNAR) for patients in the LBN 0.024% arm; and 258.2 days (APOLLO) to 92.3 days (LUNAR), for patients in the timolol maleate 0.5% crossover to LBN 0.024% arm. Study completion (both phases) was achieved by 88.0% (APOLLO) and 91.0% (LUNAR) in the LBN 0.024% arm, and by 82.7% (APOLLO) and 91.9% (LUNAR) in the crossover arm.

In the study eye, throughout both safety phases, no notable differences in mean IOP at different time points, nor in mean diurnal IOP, were observed between treatment groups. Mean IOP values fluctuated to some extent throughout the studies. In the timolol maleate 0.5% crossover to LBN 0.024% arm, in both studies, comparison between month 3 IOP values of efficacy phases and the subsequent IOP values in the safety phases may suggest a decrease in mean IOP upon treatment with LBN 0.024%. The safety phases did not analyze the proportion of patients with IOP less than or equal to 18 mm Hg, nor the proportion of patients with IOP reduction greater than or equal to 25%. In both the study eye and treated fellow eye, throughout both extension studies and between treatment arms, no differences were evident in the BCVA means nor in the proportions of normal and abnormal optic nerves.

In comparison with the efficacy phases of the two trials, no new or cumulative safety concerns emerged from the APOLLO and LUNAR extension studies. The most common ocular TEAEs reported were eye irritation, eye pain, and conjunctival hyperemia. During the LUNAR study, in both the efficacy and safety phases, the percentage of patients reporting conjunctival hyperemia in the study eye and treated fellow eye was higher in the LBN 0.024% arm than in timolol maleate 0.5% crossover to LBN 0.024% arm. In both phases of the LUNAR trial, the LBN 0.024% treatment arm experienced a higher incidence of ocular disorders. During the LUNAR safety phase, the number of new patients with ocular AEs in the timolol maleate 0.5% crossover to LBN 0.024% arm appeared to offset the difference observed between the two treatment arms in the efficacy phase. This pattern was not observed in the APOLLO trial. No notable pattern of serious adverse events (SAEs) was observed in the APOLLO or LUNAR extension studies.

The main limitations of the extension studies were the uncontrolled and unblinded nature of the safety phases.

JUPITER Study

Aim

To summarize the details and findings of the JUPITER study.[10]

Findings

Study Design

The JUPITER study was a Japanese, multi-centre, single-arm, open-label clinical study designed to assess the safety of long-term use of LBN 0.024% ophthalmic solution once daily over 12 months in patients with OAG or OHT. The study included an initial visit (visit 1), a washout period (visit 2), and a 52-week treatment period (starting at visit 3 as day 0) during which patients were assessed every four weeks. In addition to the safety analysis, the persistence of IOP reduction following long-term treatment with LBN 0.024% was assessed every four weeks from week 4 through week 52.

Population Demographics and Baseline Disease Characteristics

Patients aged 20 years and older with a diagnosis of OAG (including normal-tension glaucoma, pigmentary, or pseudoexfoliative glaucoma) or OHT in one or both eyes and a mean or median IOP ≥ 15 mm Hg and ≤ 36 mm Hg at 10:00 a.m. in at least one eye and IOP ≤ 36 mm Hg in both eyes, were included. Patients also had to have corrected decimal visual acuity or a BCVA of 0.5 or better in both eyes.

Of the patients included in this study, the mean age was 62.5 years (standard deviation [SD] of 10.87); 50.8% (n = 66) were over the age of 65 years, 43.1% (n = 56) were male, and 10.0% (n = 13) had received previous treatment. The mean corneal thickness of the study eye was 546.10 µm (SD of 31.25 µm); the majority of patients (74.6; n = 97) were in the IOP range of 15 mm Hg to 21 mm Hg. Detailed baseline demographics and disease characteristics are provided in Table 18.

Table 18: Summary of Baseline Characteristics

	LBN 0.024% (N = 130)	
Age (Years)		
Mean (SD)	62.5 (10.87)	
Median (min, max)	64.0 (39, 81)	
Age Group, n (%)		
< 65 years	66 (50.8)	
≥ 65 years	64 (49.2)	
Sex, n (%)		
Male	56 (43.1)	
Female	74 (56.9)	
Race, n (%)		
Japanese	130 (100)	
Previous Treatment, n (%)		
Yes	13 (10.0)	
No	117 (90.0)	
	Study Eye (N = 130)	**Treated Fellow Eye (N = 126)**
Mean Corneal Thickness (µm)		
Mean (SD)	546.10 (31.25)	544.35 (31.13)

	LBN 0.024% (N = 130)	
IOP Category, n (%)		
15 mm Hg to 21 mm Hg	97 (74.6)	108 (85.7)
22 mm Hg to 29 mm Hg	32 (24.6)	18 (14.3)
30 mm Hg to 36 mm Hg	1 (0.8)	0
Iris Colour, n (%)		
Brown	130 (100)	126 (100)

IOP = intraocular pressure; LBN = latanoprostene bunod; max = maximum; min = minimum; SD = standard deviation.

Source: Clinical Study Report from JUPITER.[10]

Intervention

Patients were treated with one drop of LBN 0.024% ophthalmic solution in the affected eye(s) once daily in the evening at approximately 8:00 p.m. Study drug administration was started at visit 3 (day 0) and continued to the evening before visit 16 (week 52).

Outcomes

Both ocular and systemic AEs and SAEs were assessed in patients through week 52 along with corrected visual acuity (at distance), conjunctival hyperemia, slit-lamp examination, photographs, IOP, ophthalmoscopy, visual field assessment, gonioscopy, and pachymetry. The safety population included all patients who received at least one dose of LBN 0.024% ophthalmic solution.

Efficacy (absolute and change from baseline in IOP) was assessed in both eyes using a Goldmann applanation tonometer (GAT) in the morning at 10:00 a.m. (± 30 minutes) from visit 1 (screening) to visit 16 (week 52). If both eyes were treated, the eye with the higher baseline IOP was considered the study eye and the other eye was designated as the treated fellow eye. If both eyes were treated and had the same baseline IOP, then the right eye was designated as the study eye. Efficacy analyses were based on the safety population.

Patient Disposition and Compliance

Out of 151 patients who were screened, 130 (86.1%) patients from 12 sites in Japan were included in the study, with 121 (93.1%) completing the study. The three main reasons for discontinuation included withdrawal of consent (3.1%), AEs (3.1%), and investigator decision (0.8%). Patient disposition is presented in Table 19.

Table 19: Patient Disposition

	LBN 0.024% (N = 130) n (%)
Safety population[a]	
Completed	121 (93.1)
Discontinued	9 (6.9)
Reason for discontinuation	
Withdrew consent	4 (3.1)
Adverse event	4 (3.1)
Investigator decision	1 (0.8)

LBN = latanoprostene bunod.

[a] All treated patients who received at least one dose of study drug.

Source: Clinical Study Report for JUPITER.[10]

In terms of compliance, all 130 patients returned diaries at visit 16 (week 52) and all 130 patients were between 81% and 120% compliant.

The mean duration of exposure to LBN 0.024% ophthalmic solution was 351.5 days (ranging between 28 days and 371 days), with 120 (92.3%) patients completing the study up to and beyond 52 weeks. Detailed exposure data are provided in Table 20.

Table 20: Duration of Exposure (Safety Population)

	LBN 0.024% (N = 130) n (%)
Exposure, n (%)	
Completed 1 day to ≤ 27 days (0 weeks to < 4 weeks)	0
Completed 28 days to ≤ 55 days (4 weeks to < 8 weeks)	2 (1.5)
Completed 56 days to ≤ 83 days (8 weeks to < 12 weeks)	1 (0.8)
Completed 84 days to ≤ 195 days (12 weeks to < 28 weeks)	2 (1.5)
Completed 196 days to ≤ 279 days (28 weeks to < 40 weeks)	3 (2.3)
Completed 280 days to ≤ 363 days (40 weeks to < 52 weeks)	2 (1.5)
Completed ≥ 364 days (≥ 52 weeks)	120 (92.3)
Duration of Exposure (Days), n	130
Mean (SD)	351.5 (59.30)
Median (min, max)	364.0 (28, 371)

LBN = latanoprostene bunod; max = maximum; min = minimum; SD = standard deviation.

Source: Clinical Study Report for JUPITER.[10]

Efficacy

Intraocular Pressure

Mean baseline IOP in the study eye (n = 130) was 19.56 mm Hg (SD: 2.875 mm Hg). The mean IOP in week 52 for 121 patients was 14.42 mm Hg (SD: 2.672 mm Hg), with a statistically significant IOP reduction from baseline of 5.25 mm Hg (SD: 2.633 mm Hg; *P* < 0.001). Approximately 47% of patients had a reduction of at least 5 mm Hg at week 52. In addition, no patients were withdrawn from the study for having an IOP greater than 36 mm Hg while taking LBN 0.024% ophthalmic solution once daily. Detailed efficacy results are presented in Table 21.

Table 21: Reduction From Baseline of Intraocular Pressure in the Study Eye (Safety Population)

	LBN 0.024% (N = 130)
Baseline, n	130
IOP[a] (SD)	19.56 (2.88)
Median (min, max)	19.00 (15.0, 30.0)
Week 52, n	121
IOP[a] (SD)	14.42 (2.67)
Reduction from baseline[b] (SD)	5.25 (2.63)
P value[c]	< 0.001

IOP = intraocular pressure; LBN = latanoprostene bunod; max = maximum; min = minimum; SD = standard deviation.

[a] Original absolute IOP assessment value.

[b] Reduction from baseline IOP = baseline IOP value – post-baseline absolute IOP value.

[c] *P* value from one sample t-test on reduction from baseline.

Source: Clinical Study Report for JUPITER.[10]

Harms

Of the 130 patients in the safety population, 76 (58.5%) of patients experienced at least one ocular AE in their study eye. The most common AEs were conjunctival hyperemia (17.7%; n = 23), growth of the eyelashes (16.2%; n = 21), eye irritation (11.5%; n = 15), and eye pain (10.0%; n = 13). Ocular AEs in the study eyes were rated as mostly mild (56.2% of patients) or moderate (2.3% of patients).

For the 126 patients who had both eyes treated, 78 (61.9%) of patients experienced at least one ocular AE in the treated fellow eye. The most common AEs were conjunctival hyperemia (16.7%; n = 21), growth of the eyelashes (16.7%; n = 21), eye irritation (11.9%; n = 15), and eye pain (10.3%; n = 13). Ocular AEs in the treated fellow eyes were rated as mostly mild (60.3% of patients) or moderate (1.6% of patients).

Eight patients (6.2%) experienced SAEs; however, none were determined to be related to LBN 0.024% ophthalmic solution. In addition, no deaths occurred. Detailed harms are presented in Table 22, including notable harms specific to this review and non-ocular AEs.

Table 22: Harms

	LBN 0.024% (N = 130)	
AEs, n (%)		
Non-Ocular AEs		
Patients with > 0 AEs	67 (51.5)	
Most common AEs[a]		
Gastrointestinal disorders	12 (9.2)	
Dental caries	2 (1.5)	
Diarrhea	2 (1.5)	
Gastric polyps	2 (1.5)	
Gastritis atrophic	2 (1.5)	
Infections and infestations	47 (36.2)	
Influenza	5 (3.8)	
Nasopharyngitis	42 (32.3)	
Musculoskeletal and connective tissue disorders	12 (9.2)	
Back pain	2 (1.5)	
Osteoporosis	3 (2.3)	
Skin and subcutaneous tissue disorders	7 (5.4)	
Eczema	4 (3.1)	
Vascular disorders	2 (1.5)	
Hypertension	2 (1.5)	
Ocular AEs	**Study Eye (N = 130)**	**Treated Fellow Eye (N = 126)**
Patients with > 0 AEs	76 (58.5)	78 (61.9)
Patients with > 0 TAE	62 (47.7)	61 (48.4)
Eye disorders[a]	76 (58.5)	78 (61.9)
Asthenopia	3 (2.3)	2 (1.6)
Blepharal pigmentation	4 (3.1)	4 (3.2)
Blepharitis	3 (2.3)	3 (2.4)
Cataract	1 (0.8)	3 (2.4)
Chalazion	0	2 (1.6)
Conjunctival hemorrhage	2 (1.5)	3 (2.4)
Conjunctival hyperemia	23 (17.7)	21 (16.7)
Eye irritation	15 (11.5)	15 (11.9)
Eye pain	13 (10.0)	13 (10.3)
Eye pruritus	3 (2.3)	3 (2.4)
Foreign body sensation in eyes	2 (1.5)	1 (0.8)
Growth of eyelashes	21 (16.2)	21 (16.7)
Hordeolum	1 (0.8)	3 (2.4)
Iris hyperpigmentation	5 (3.8)	5 (4.0)
Punctate keratitis	3 (2.3)	2 (1.6)
Trichiasis	3 (2.3)	2 (1.6)
Visual impairment	1 (0.8)	2 (1.6)
Vitreous floaters	1 (0.8)	2 (1.6)

	LBN 0.024% (N = 130)	
Notable Harms		
Macular edema	-	-
Iris hyperpigmentation	5 (3.8)	5 (4.0)
Conjunctival hyperemia	23 (17.7)	21 (16.7)
Eye irritation	15 (11.5)	15 (11.9)
Eye pain	13 (10.0)	13 (10.3)
Eye dryness	1 (0.8)	1 (0.8)
Hypopigmentation of eyelid	1 (0.8)	1 (0.8)
SAEs		
Patients with > 0 SAEs	8 (6.2)	
WDAEs		
n (%)	2 (1.5)	
Deaths		
n (%)	0	

AE = adverse event; LBN = latanoprostene bunod; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency ≥ 1%.

Source: Clinical Study Report for JUPITER.[10]

Limitations

Key limitations associated with this study include the uncontrolled and open-label nature of the study and the lack of a comparator arm. This limits the ability to ascertain the true efficacy and safety associated with using LBN 0.024% ophthalmic solution once daily in the long term, since only descriptive statistics (as opposed to true statistical comparisons) were provided. In addition, while the attrition rate was small, there was still no discussion pertaining to what was done with the missing data.

The major limitation associated with the external validity of this study pertains to the inclusion of only Japanese patients. There are anatomical differences with the eyes (particularly the eyelids) of Japanese patients when comparing them with other races, and IOP measurements using GAT have been shown to be increased in Asian patients due to the smaller palpebral fissure height and subsequent manual manipulation of the eyelid.[38]

Summary

The JUPITER study was an open-label, uncontrolled, single-arm Japanese study designed to assess the long-term safety and efficacy of LBN 0.024% ophthalmic solution once daily in one or both eyes of patients with OAG or OHT. The mean duration of treatment was 351.5 days, with 92.3% of patients completing at least 364 days of treatment. The mean IOP in week 52 (n = 121) was 14.42 mm Hg, with a statistically significant reduction of IOP from baseline of 5.25 mm Hg. In addition, approximately 47% of patients had a reduction of at least 5 mm Hg after one year of treatment.

Between 58% and 70% of patients experienced AEs in the study eye and fellow treated eye, respectively. The most common AEs were conjunctival hyperemia, growth of the eyelashes, eye irritation, and eye pain, with most AEs being mild in nature.

This study remains primarily descriptive in nature due to the lack of a comparator arm and its uncontrolled, open-label nature. In addition, the results from this study cannot necessarily be generalized to patients of other races due to the anatomical differences of the eyelids of Japanese patients, who often have increased IOP measurements because of the manual manipulation needed to perform GAT measurements.

Appendix 7: Summary of Indirect Comparisons

Introduction

[redacted]

Methods

Objectives and Rationale for Manufacturer's Indirect Treatment Comparison

[redacted]

Study Eligibility and Selection Process

Literature Search

[redacted]

Table 23: Population, Interventions, Comparisons, Outcomes, and Study Design Criteria for Study Inclusion

Criteria	Monotherapy
Population	[redacted]
Interventions	[redacted]
Comparators	[redacted]
Outcomes	[redacted]
Study Design and Factors	[redacted]
Language	[redacted]
Search Period	[redacted]

Source: Manufacturer's submitted indirect treatment comparisons.[39]

Eligibility Criteria and Study Selection

[redacted]

Data Extraction

[redacted]

Comparators

[redacted]

[redacted]

Outcomes

[redacted]

Quality Assessment of Included Studies

[redacted]

Indirect Comparison Methods

[redacted]

[redacted]

[redacted]

Results

[redacted]

[redacted]

[redacted]

Table 24: Summary of Studies Included and Baseline Characteristics

Characteristics	N
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: Manufacturer's submitted indirect treatment comparisons.[39]

Table 25: Summary of Baseline Characteristics by Treatment

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Source: Manufacturer's submitted indirect treatment comparisons.[39]

Figure 3: Network of Trials Included in Network Meta-Analysis

[redacted] This figure has been redacted.

Source: Manufacturer's submitted indirect treatment comparisons.[39]

Table 26: Studies Identified as Possibly Causing Heterogeneity

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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Source: Manufacturer's submitted indirect treatment comparisons.[39]

Analysis Results

[redacted]

[redacted]

Figure 4: Relative Effect from the Indirect Comparison of Intraocular Pressure Reductions for Treatment Assessment in Glaucoma (With the 95% Credible Interval)

This figure has been redacted.

[redacted]

Source: Manufacturer's submitted indirect treatment comparisons.[39]

Figure 5: Ranking Probability of Any Drug Being Most Efficacious

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[redacted]

Source: Manufacturer's submitted indirect treatment comparisons.[39]

Critical Appraisal

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Conclusion

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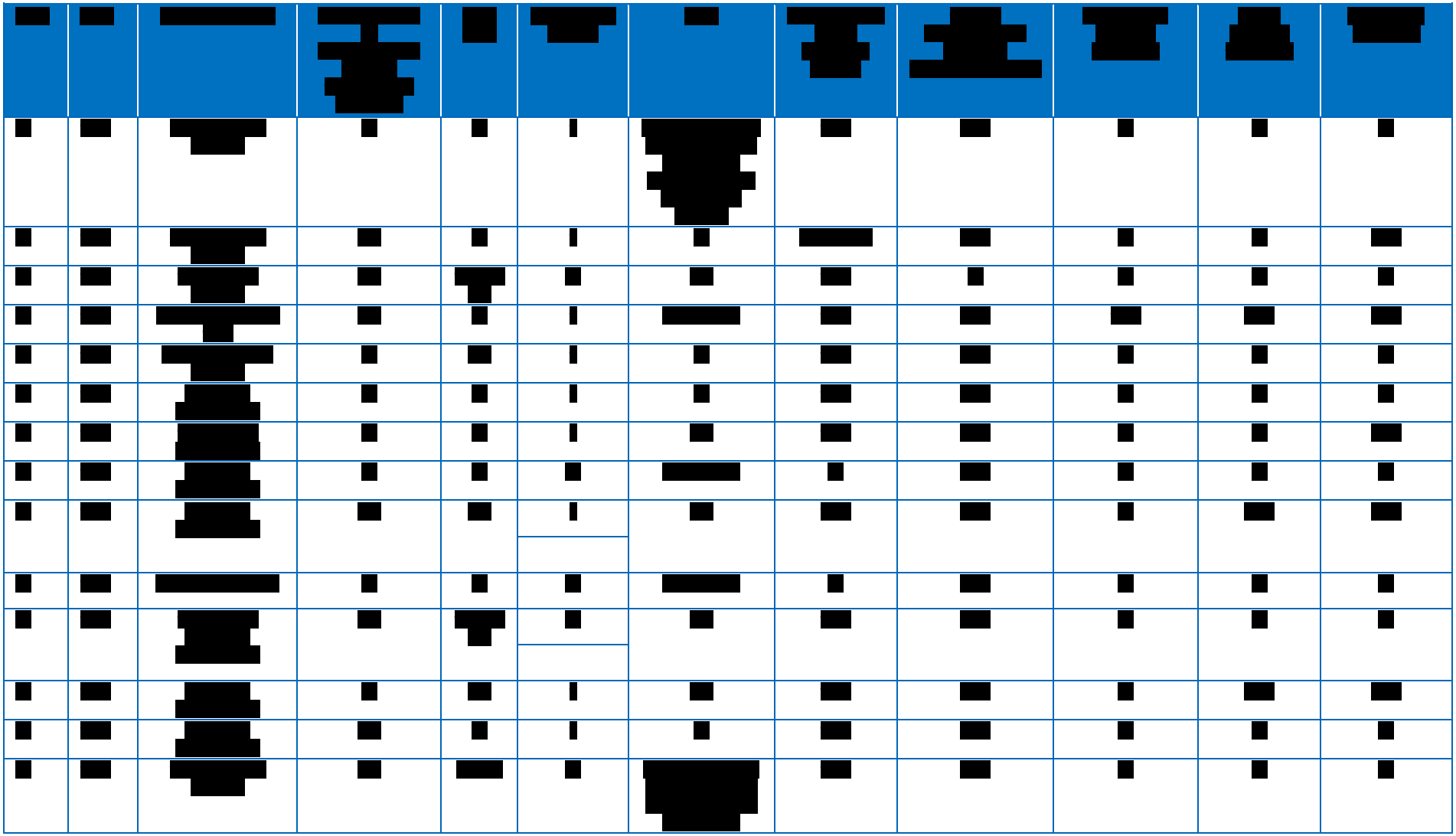
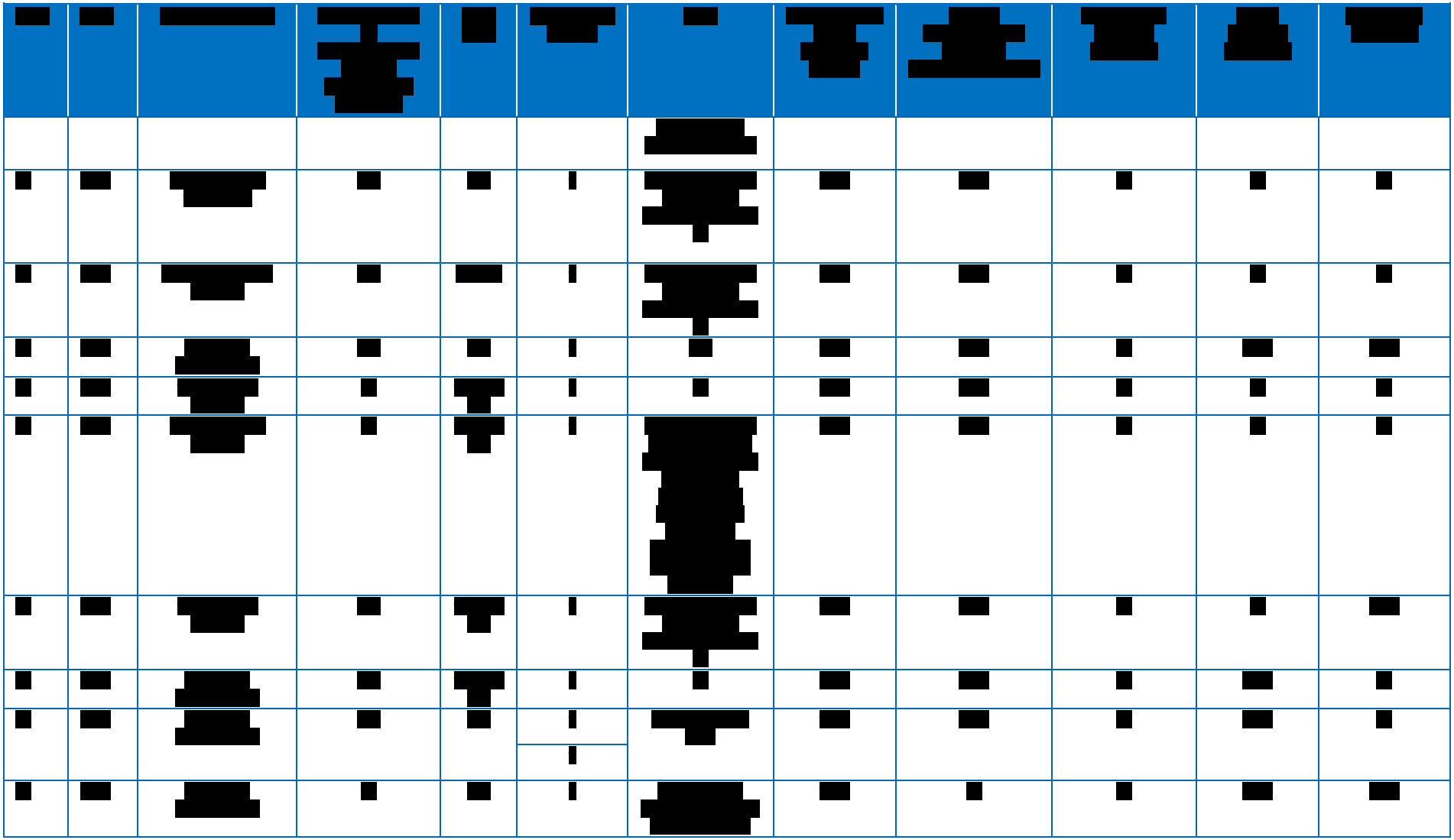
Table 27: Baseline Patient Demographic and Clinical Characteristics of Included Randomized Controlled Trials

[redacted]											





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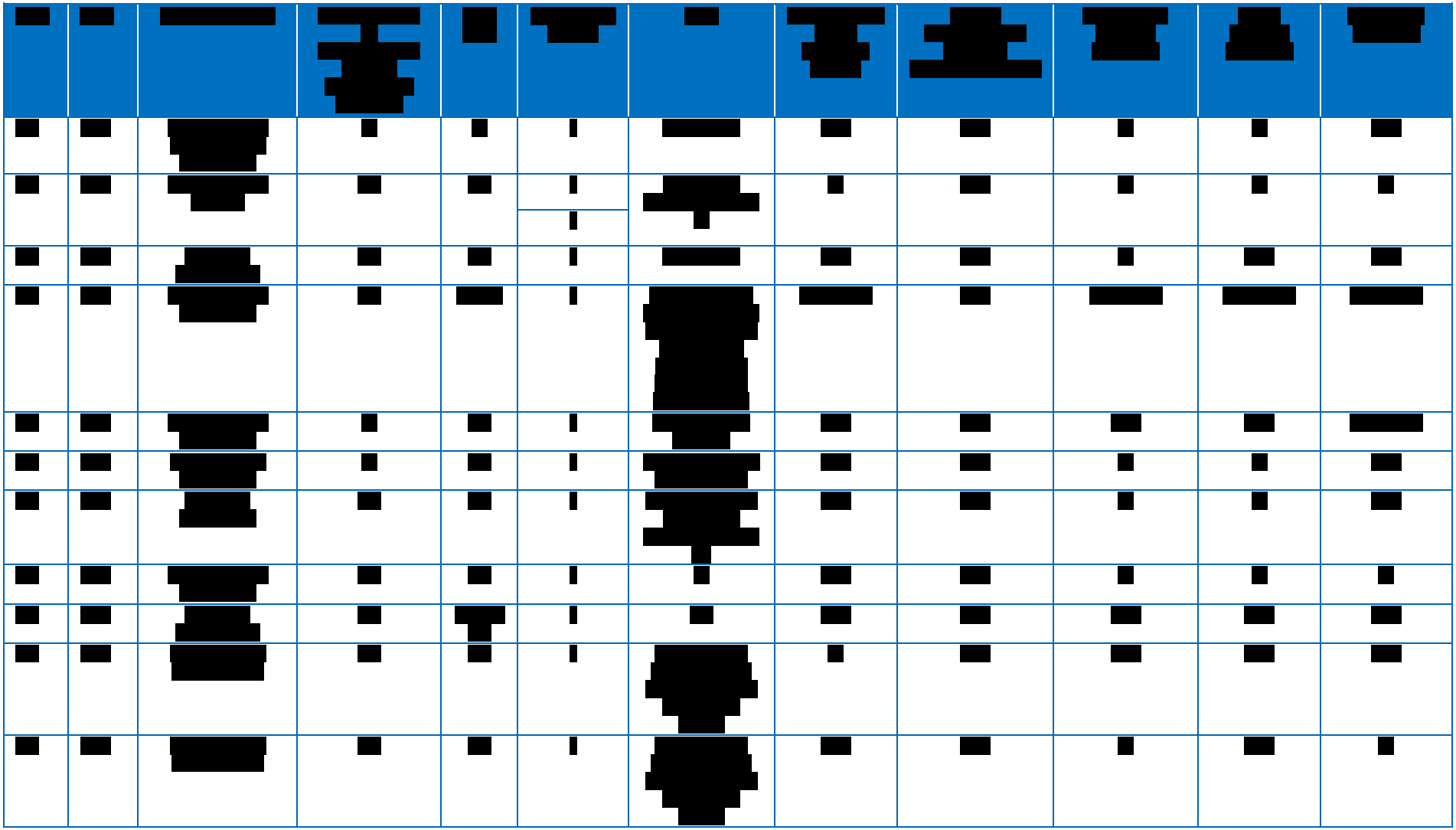

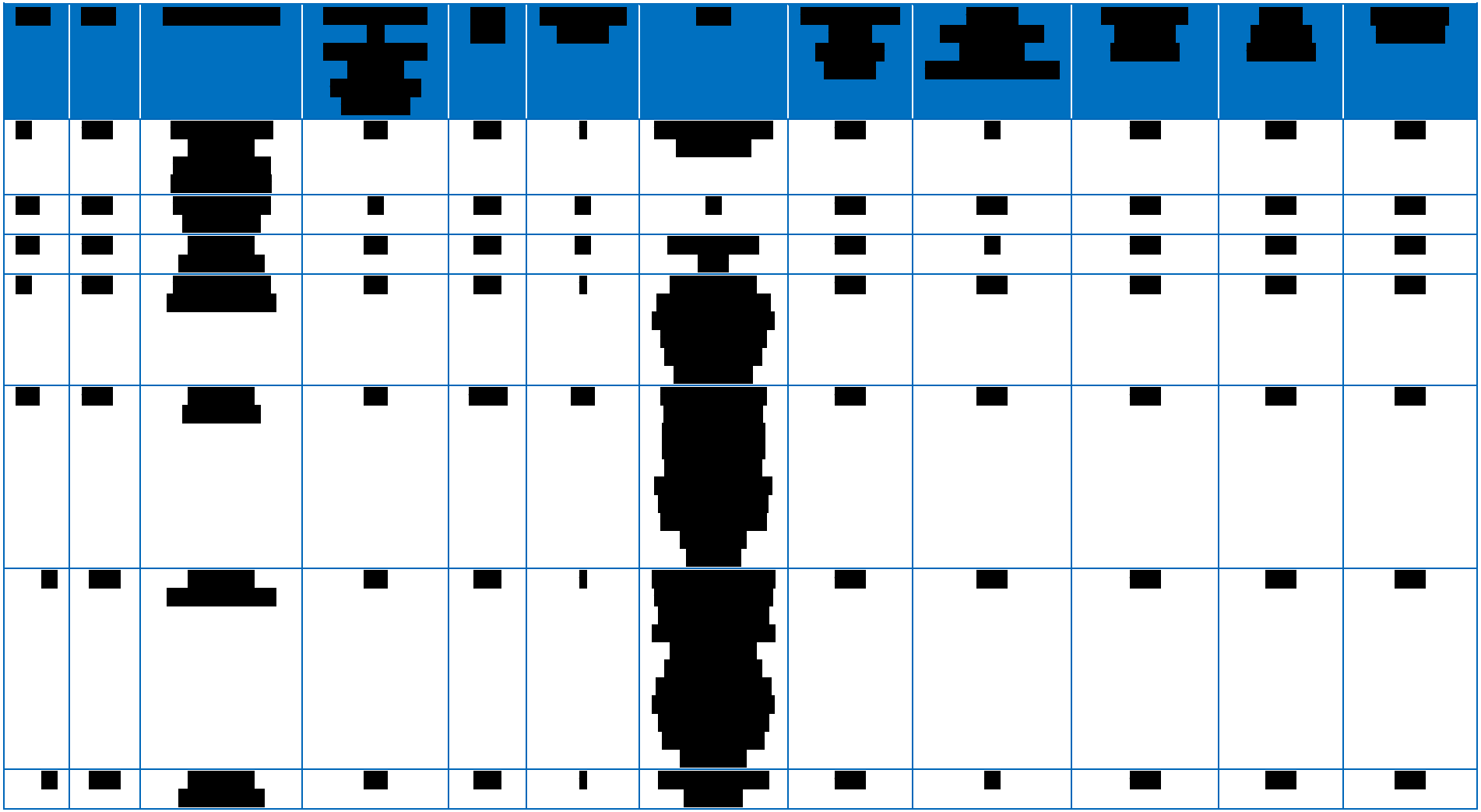

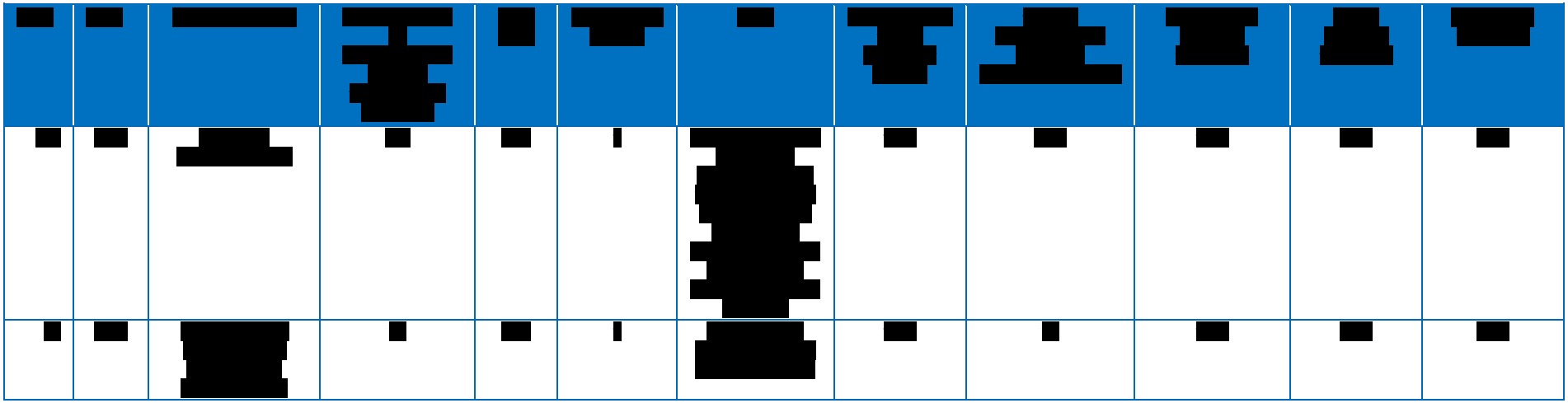

Source: Manufacturer's submitted indirect treatment comparisons.[39]

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