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CADTH COMMON DRUG REVIEW

Clinical Review Report

Preservative-free latanoprost 50 µg/mL ophthalmic solution (Monoprost)

(Laboratoires Théa)

Indication: Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

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Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BAK	benzalkonium chloride
CI	confidence interval
CDR	CADTH Common Drug Review
IOP	intraocular pressure
ITT	intention-to-treat
LOCF	last observation carried forward
MCID	minimal clinically important difference
OAG	open-angle glaucoma
OSD	ocular surface disease
PGA	prostaglandin analogue
PP	per-protocol
RCT	randomized controlled trial
SD	standard deviation

Drug	Preservative-free latanoprost (Monoprost)
Indication	Reduction of intraocular pressure in patient with open-angle glaucoma or ocular hypertension
Reimbursement request	As per indication
Dosage form	Solution / 50 µg/mL
NOC date	2016-07-07
Manufacturer	Laboratoires Théa

Executive Summary

Introduction

Glaucoma is a term that refers to a group of optic neuropathies that, together, form the leading cause of irreversible blindness worldwide.[1] The self-reported prevalence of glaucoma from 2002 to 2003 in Canada was an estimated 2.7% in those 40 years and older and 11% in those 80 years and older.[2] Glaucoma is characterized by the loss of retinal nerve fibres and changes in the optic disc.[3] As glaucoma progresses and the optic nerve head is damaged, there is a resulting loss of the peripheral visual field, followed by loss of visual acuity, which may progress to blindness.[4] The most prevalent type of primary glaucoma is open-angle glaucoma (OAG). Elevated intraocular pressure (IOP) is an important risk factor for glaucoma, which is staged based on IOP, optic disc features, and visual field defects.[3] For most individuals, the normal range of IOP is between 10 mm Hg and 21 mm Hg.[4] Ocular hypertension may be present in the absence of glaucomatous damage to the optic disc or visual field loss, and only a minority of patients with elevated IOP develop glaucoma.[1,3,4]

Lowering IOP is the only clinically established method of treating glaucoma, and the Canadian Ophthalmological Society's clinical practice guidelines for glaucoma recommend an initial target IOP based on the severity of glaucoma, to be modified based on patients' age, life expectancy, quality of life, and risk factors for progression.[3] Pharmacologic therapy is the most common method of lowering IOP, and the most common first-line therapy in Canada is topical prostaglandin analogues (PGAs), including latanoprost.[3] Since patients with OAG require lifetime therapy, they are at greater risk of ocular surface disease (OSD), which is associated with the long-term use of topical ophthalmic antiglaucoma medications.[5] Patients with OSD may experience dry eye or sensations of burning, stinging, itching, or discomfort in the eye.[5] Preservatives in topical ophthalmic solutions, of which the most common is benzalkonium chloride (BAK), have been implicated in OSD.[5] Glaucoma medical therapy is often characterized by nonadherence, and the availability of preservative-free PGAs would address an unmet need for patients who do not tolerate preserved PGAs well. The objective of this report is to perform a systematic review of the beneficial and harmful effects of preservative-free latanoprost 50 µg/mL ophthalmic solution (Monoprost) for the reduction of IOP in patients with OAG or ocular hypertension.

Results and Interpretation

Included Studies

The two studies included in the systematic review, LT2345-PIII-12/08[6,7] and LT2345-001,[8] were phase III RCTs sponsored by the manufacturer. Both RCTs had a parallel-groups design with masking of the investigators but not the patients. Both studies compared Monoprost monotherapy with Xalatan (i.e., BAK-preserved latanoprost) monotherapy for efficacy in lowering IOP, safety, and tolerance in patients with OAG or ocular hypertension already controlled by latanoprost monotherapy. LT2345-PIII-12/08 (N = 404)[6] was a pivotal study designed to demonstrate noninferiority of Monoprost to Xalatan in lowering elevated IOP, conducted in 63 centres in Europe (including 42 centres in France) and 13 centres in Tunisia. LT2345-001 (N = 334)[8] was a supportive study designed to demonstrate equivalent IOP-lowering efficacy of Monoprost and Xalatan, conducted in 31 centres in the US. Monoprost was provided in single-dose units, and Xalatan was provided in multi-dose containers.

In the pivotal study, only a small proportion of patients had glaucoma (2% and 5% in the Monoprost and Xalatan groups) and less than 1% had OAG. In the supportive study, 12% and 19% of patients in the Monoprost and Xalatan groups, respectively, had abnormal visual field with glaucomatous defect in the study eye. Summaries of medical and surgical history were not available for the supportive study. Prevalence of eye dryness sensation, irritation/burning/stinging, itching, tearing, foreign body sensation, and photophobia was similar between treatment groups in the pivotal study, with each symptom affecting 7% or less of patients in each group. Mean baseline IOP was 24.1 mm Hg and 24.0 mm Hg (following four weeks of latanoprost washout) in the pivotal study's Monoprost and Xalatan groups, respectively, while mean diurnal baseline IOP in the supportive study was 18.8 mm Hg and 19.2 mm Hg in the Monoprost and Xalatan groups, respectively (following at least 72 hours of latanoprost washout). Duration of ocular hypertension or OAG and previous medication history was not reported.

The only concomitant ocular treatment permitted in both studies was unpreserved artificial tears. In the pivotal study, systemic treatments were permitted only if the dosage regimen was unchanged for at least one month before screening. In the supportive study, intranasal and inhaled steroids were permitted, as well as systemic beta blockers or calcium channel blockers, provided the dosage regimen was unchanged for more than three months before screening.

The primary efficacy end point was the change in IOP from baseline to day 84 in the pivotal study and from baseline to days 15, 42, and 84 in the supportive study. IOP was measured at 9:00 a.m. in the pivotal study, while IOP was measured at 8:00 a.m., 10:00 a.m., and 4:00 p.m. in the supportive study. The noninferiority margin was defined as 1.5 mm Hg in the pivotal study. For the supportive study, the 95% confidence interval (CI) for the difference in IOP change had to be within –1.5 mm Hg to 1.5 mm Hg for all measurements and within –1.0 to 1.0 mm Hg for at least five of the nine post-baseline IOP measurements.

Tolerability and safety end points were evaluated in the safety population. Conjunctival hyperemia is redness in the conjunctiva — the membrane covering the front of the eye and lining the inner surface of the eyelids — resulting from vasodilation of the conjunctival vessels. In both studies, investigators rated severity of conjunctival hyperemia on the photographic McMonnies scale, and patients reported severity of symptoms of ocular discomfort upon instillation of study medication (i.e., pruritus, burning/stinging, blurred

vision, sticky eye sensation, eye dryness sensation, or foreign body sensation) on a four-point ordinal scale ranging from 0 or “none” to 3 or “very disturbing.” In the pivotal study, patients also reported severity of ocular symptoms (i.e., eye dryness sensation, foreign body sensation, irritation/burning/stinging, itching, photophobia, tearing) at least one hour before or after instillations of study medication. Abnormalities observed in various parts of the anterior segment of the eye under slit-lamp examination and their severity, as well as visual acuity, were reported.

Because of the single-masked nature of the studies, there was some risk of bias in patient-reported outcomes, such as ocular symptoms and adverse events. Measurements of treatment compliance were based on patient recall, and drug accountability was affected by the fact that it was easier to count returned single-dose Monoprost units than multi-dose bottles of Xalatan, which were not weighed.

Two additional relevant studies were excluded from the systematic review owing to study design, and these are summarized in the Appendices. A phase IV, open-label study[9] compared efficacy and tolerability of Monoprost and Xalatan, and a meta-analysis of indirect comparisons[10] assessed Monoprost against other PGAs for efficacy and occurrence of conjunctival hyperemia. Both studies evaluated end points three months after baseline, identical to the follow-up period in the phase III RCTs.

Efficacy

Results from the pivotal and supportive phase III RCTs indicated that efficacy in IOP lowering is similar between Monoprost and Xalatan (Table 1). Noninferiority in efficacy of Monoprost to Xalatan was established in the pivotal study. In the supportive study, the main analysis for equivalence in mean change in IOP between Monoprost and Xalatan met the 1.5 mm Hg criterion but not the 1.0 mm Hg criterion for most measurements. Analysis of IOP change in the contralateral eye, which was the eye with the higher IOP at baseline, met both equivalence criteria, with five out of nine measurements meeting the 1.0 mm Hg margin. The mean between-group differences were less than 1.0 mm Hg and were not considered clinically important by the clinical expert consulted for this review.

Patients in the pivotal and phase IV studies had been on latanoprost monotherapy for at least nine months before the pivotal study and six months before the phase IV study and were therefore known to respond to the active ingredient in both study drugs. The majority of patients in the phase III studies had ocular hypertension, rather than glaucoma, although the clinical expert consulted for this review indicated that disease status alone would not have affected response to the drugs in terms of efficacy, tolerability, and safety.

The results from the indirect treatment comparison meta-analysis indicated that IOP after three months of study treatment was similar between Monoprost and bimatoprost 0.03% and between Monoprost and bimatoprost 0.01%, with mean differences of less than 0.5 mm Hg and 95% confidence intervals overlapping zero. Given the similarity in efficacy between Monoprost and Xalatan in the phase III RCTs, these results were consistent with previous studies that showed similar IOP-lowering efficacy among the PGAs and greater efficacy with bimatoprost 0.03% in some cases.[11] However, there were several limitations identified with the meta-analysis.

Tolerability and Safety

Tolerability and safety outcomes were assessed in the safety set for the phase III and IV studies; however, statistically significant findings should be interpreted with caution due to lack of control for multiplicity.

Regardless of treatment group, most patients had the lowest score (1 or “hyperemia not present”) for conjunctival hyperemia severity, and no patients had the greatest severity scores (5 and 6). The difference in score distributions between groups was most pronounced at days 42 and 84 (*P* values of 0.003 and 0.019, respectively), with absolute differences in each category ranging from 1% to 7% in favour of Monoprost. In the supportive study, no difference was found between groups for mean score. According to the clinical expert consulted for this review, different patients have different thresholds for severity of conjunctival hyperemia considered to be intolerable. Therefore, the clinical importance of the results for investigator-assessed conjunctival hyperemia is uncertain in the phase III studies.

Severity of conjunctival hyperemia assessed on the Efron scale in the phase IV study was reduced to a greater extent in the Monoprost group, although there were no patients in the highest category of severity and the clinical importance of the mean score reduction of 0.5 in the Monoprost group was unclear. Unlike in the phase III studies, investigators were not blinded to treatment allocation, and bias in hyperemia assessment was possible.

At each post-baseline visit in the pivotal study, less than 4% of patients in each treatment group rated ocular symptoms upon instillation as “disturbing” or “very disturbing.” While consistently lower percentages of patients had “disturbing” and “very disturbing” burning/stinging ($P \leq 0.006$ for the score distributions at each visit) in the Monoprost group, the differences in these categories were small. Similar results were observed for the symptom of irritation/burning/stinging between instillations. At each post-baseline visit in the supportive study, fewer than 2% of patients in each treatment group reported “disturbing” or “very disturbing” for each ocular symptom upon instillation.

In the phase IV study, patients in the Monoprost group had larger reductions (absolute reductions of 6% to 23%) in proportions of those with symptoms, especially in dryness, irritation/tingling/burning, and foreign body sensation. More patients in the Xalatan group had changed medication in the previous five years (43% versus 32%), and they may have been more likely to report ocular symptoms.

In the pivotal study, based on patient recall, compliance with study medication was numerically lower in the Monoprost group (78% and 82%) than in the Xalatan group (93% and 91%) at the day 42 and 84 visits, although mean compliance based on amount of drug instilled was similar between the groups (98.4% to 99.7%). All of the six patients reporting less than 70% compliance (based on days with drug instillation) were in the Monoprost group, with compliance ranging from 50% to 65% between visits for these patients.

No notable differences were found between groups in the phase III studies for ocular signs and abnormalities or visual acuity.

The indirect comparisons showed lower proportions of patients with hyperemia or ocular redness with Monoprost than with sofZia-preserved travoprost, bimatoprost 0.03%, and bimatoprost 0.01%. Odds ratios ranged from 0.18 to 0.37, and confidence intervals

excluded the value 1. Pooling of hyperemia estimates was likely inappropriate, as the outcome was not well defined.

Harms

There were no safety concerns raised in the phase III studies or the phase IV study, and withdrawals due to adverse events (AEs) were very limited. AEs were more commonly reported in the phase III studies (9% to 23% of patients) than in the phase IV study (2% to 4% of patients). The most common types of AEs were pain at the instillation site, conjunctival hyperemia, and punctate keratitis. Some AEs were more common in the Xalatan groups, although the numbers of events were very low for all the AEs. The clinical expert consulted for this review considered the AEs reported to be typical of this patient population and drug class. Because patient knew their treatment allocation, bias in AE reporting could not be ruled out.

Potential Place in Therapy[1]

As of 2018, the standard of care for the treatment of glaucoma is to reduce IOP, which is most often done with medications. There are several different classes of medications used to lower IOP, with the most common being PGAs. Most of the PGAs available in Canada are preserved with BAK, with the exception of Travatan Z, sofZia-preserved travoprost 0.004%, and Izba, polyquaternium-1–preserved travoprost 0.003%.

OSD includes a variety of conditions that affect the surface of the eye, notably the cornea and conjunctiva. OSD is common, affecting 15% of patients over 65.[12] However, in patients receiving glaucoma medical therapy, a prevalence of up to 60% has been reported.[13] OSD affects vision-related quality of life and may negatively affect compliance with glaucoma medical therapy. Inflammatory changes from OSD may negatively affect subsequent surgical outcomes. There is a lack of widely accepted criteria for diagnosing OSD, and correlation between clinical tests and OSD symptoms has been poor.[13]

The causes of OSD are multifactorial and include dry eye, blepharitis, and rosacea. However, OSD can also be caused or exacerbated by eye drops. The toxic or allergic effects from eye drops could be due to any of the constituents, including the active ingredient, the excipients, and/or the preservative. Since BAK is known to be cytotoxic, and long-term use of BAK can result in changes to the surface of the eye and exacerbate symptoms of OSD, the availability of a BAK-free PGA such as Monoprost could fill an unmet need.

However, the safety profiles of Travatan Z and Izba (preserved with alternatives to BAK) are similar to the safety profile of BAK-preserved travoprost in terms of OSD symptoms reported as AEs,[14,15] suggesting that BAK may have only a limited role in OSD. The currently marketed BAK-free PGAs do not appear to fulfill the unmet need for the reduction of OSD symptoms.

With its higher price, Monoprost would need to demonstrate a significant reduction in OSD symptoms over other PGAs to be considered as a first-line treatment for the reduction of IOP in patients with no contraindications to a PGA. Given the lack of such evidence, it could be considered as a second-line PGA for patients unable to tolerate a PGA because of severe OSD.

1 This information is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review reviewers for the purpose of this review.

Conclusions

Results from the two included phase III studies showed similar IOP-lowering efficacy of Monoprost when compared with Xalatan (i.e., BAK-preserved latanoprost) over a period of three months. Similar results were shown in an open-label phase IV study. An indirect treatment comparison meta-analysis indicated similar IOP-lowering efficacy of Monoprost compared with bimatoprost (both the 0.03% and 0.01% formulations), although the study had limitations. Direct or indirect comparisons of IOP outcomes of Monoprost versus other comparators currently available in Canada were not available.

Assessment of conjunctival hyperemia and symptoms of ocular discomfort in the phase III studies and phase IV study suggested favourable tolerability of Monoprost compared with Xalatan. However, there were limitations in the outcomes reported and small differences between treatment groups, meaning that the benefits of Monoprost were uncertain and of unclear clinical importance. The indirect treatment comparisons also suggested lower incidence of conjunctival hyperemia with Monoprost compared with sofZia-preserved travoprost and BAK-preserved bimatoprost, but these results were associated with limitations. While some AEs were more common in the Xalatan group than in the Monoprost group, the proportions of patients with each AE were low (5% or less). Visual acuity and the incidence of abnormalities in the anterior segment of the eye did not differ between the Monoprost and Xalatan groups. There was no evidence of differences in treatment compliance between the Monoprost and Xalatan groups.

Table 1: Summary of Results

	Study LT2345-PIII-12/08		Study LT2345-001	
Intraocular Pressure	**Monoprost N = 189 mITT Set**	**Xalatan N = 164 mITT Set**	**Monoprost N = 161 PP Set**	**Xalatan N = 164 PP Set**
Study eye IOP[a], mm Hg, mean (SD)				
Baseline	24.1 (1.8)	24.0 (1.7)	18.8 (2.9)	19.2 (3.1)
Day 84	15.4 (2.3)	15.0 (2.0)	16.3 (2.6)	15.7 (2.5)
Change from baseline to day 84, mean (95% CI)	–8.6 (–9.0 to –8.3)	–9.0 (–9.4 to –8.7)	–2.6 (–3.0 to –2.2)	–3.4 (–3.8 to –3.1)
Difference in change, Monoprost versus Xalatan, mean (95% CI)	0.42 (0.00 to 0.84)[b] Noninferiority margin of 1.5 mm Hg met		0.68 (0.28 to 1.09)[c,d]	
Tolerability and Harms	**Monoprost N = 213 Safety Set**	**Xalatan N = 189 Safety Set**	**Monoprost N = 164[e] Safety Set**	**Xalatan N = 167[e] Safety Set**
Investigator's assessment of conjunctival hyperemia (McMonnies photographic scale) in the study eye, day 84, *P* value[f]				
% of patients[e], score = 2 / 3 to 4 / 5 to 6	17 / 5 / 0	22 / 8 / 0	NR	NR
	P = 0.019			
Change from baseline in mean score, LSM difference, Monoprost versus Xalatan[g]	NR		–0.061, *P* = 0.49	
% of patients with disturbing or very disturbing ocular symptoms upon instillation, day 84, *P* value[f]				
Pruritus	0	2.2, *P* = 0.10	1.9	0
Burning/stinging	0.5	3.2, *P* < 0.001	0.6	0.6
Blurred vision	0.5	2.7, *P* = 0.24	1.2	0
Sticky eye sensation	0	0, *P* = 0.77	0	0
Eye dryness sensation	0	0, *P* = 0.96	1.2	0

	Study LT2345-PIII-12/08		Study LT2345-001	
Foreign body sensation	0.5	0, *P* = 0.46	1.9	0
Subjects with ≥ 1 ocular SAE, n	0	0	0	0
Subjects with ≥ 1 systemic SAE, n (%)	5 (2)	1 (0.5)	1 (0.6)	4 (2)
Ocular WDAE, n (%)	2 (0.9)	1 (0.5)	1 (0.6)	1 (0.6)
Systemic WDAE, n (%)	1 (0.5)	1 (0.5)	0	2 (1)
Notable harms, n (%)				
Blepharitis	1 (0.5)	0	2 (1)	5 (3)
Conjunctival hyperemia	1 (0.5)	3 (2)	3 (2)	4 (2)
Drug intolerance	1 (0.5)	4 (2)	NR	NR
Dry eye	1 (0.5)	2 (1)	1 (0.6)	1 (0.6)
Foreign body sensation in eyes	1 (0.5)	2 (1)	1 (0.6)	0
Instillation site pruritus	NR	NR	2 (1)	1 (0.6)
Photophobia	1 (0.5)	2 (1)	0	1 (0.6)
Punctate keratitis	1 (0.5)	2 (1)	1 (0.6)	5 (3)
Vision blurred	1 (0.5)	3 (2)	1 (0.6)	0
Eye irritation	1 (0.5)	1 (0.5)	0	1 (0.6)
Eye pruritus	2 (0.9)	1 (0.5)	1 (0.6)	1 (0.6)
Lacrimation increased	0	1 (0.5)	1 (0.6)	0

CI = confidence interval; IOP = intraocular pressure; LSM = least squares mean; mITT = modified intention-to-treat; NR = not reported; PP = per-protocol; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

Note: If both eyes were eligible, study eye was the eye with higher baseline IOP in LT2345-PIII-12/08 and the eye with lower baseline IOP in LT2345-001. If both eyes had the same baseline IOP, the right eye was the study eye.

[a] IOP was measured at 9:00 a.m. for LT2345-PIII-12/08. IOP presented here for LT2345-001 was the average of measurements at 8:00 a.m., 10:00 a.m., and 4:00 p.m.

[b] Mixed-effects model for repeated measures adjusted for baseline IOP, country, visit, treatment-by-visit interaction, and baseline IOP-by-visit interaction.

[c] Analysis of covariance on change from baseline adjusted for pooled site and baseline IOP.

[d] Equivalence criterion 1: All measurements of change in IOP from baseline (at 8:00 a.m., 10:00 a.m., and 4:00 p.m. on days 15, 42, and 84) meet a 1.5 mm Hg equivalence margin (criterion was met). Equivalence criterion 2: At least five of the nine measurements meet a 1.0 mm Hg equivalence margin (criterion was not met).

[e] Patients with available data.

[f] Cochran–Mantel–Haenszel test stratified by country. Analysis was done on numbers of patients in each of the categories of severity.

[g] Analysis of covariance on change from baseline adjusted for pooled site and baseline value.

Source: Clinical Study Reports.[6,8]

Introduction

Disease Prevalence and Incidence

Glaucoma is a term that refers to a group of optic neuropathies, which together form the leading cause of irreversible blindness worldwide.[1] Glaucoma is characterized by a loss of retinal nerve fibres and changes in the optic disc.[3] The optic nerve head is damaged, and there is irreversible loss of visual field.[4] As glaucoma progresses, there is resulting loss of the peripheral visual field, followed by loss of visual acuity, which may progress to blindness.[4] It is associated with high intraocular pressure (IOP), although up to 50% of patients with glaucoma have IOP within the normal range (10 mm Hg to 21 mm Hg).[4] The main risk factors for glaucoma are elevated IOP, age, family history, and race.[3]

Glaucoma can be staged as a suspect, early, moderate, or advanced, depending on IOP, optic disc features, and visual field defects.[3] IOP is dependent on secretion of aqueous humour by the ciliary body as well as drainage of aqueous humour from the eye through the trabecular meshwork and uveoscleral outflow pathway.[1] The most prevalent type of primary glaucoma 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.[4] 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.[1,4]

However, ocular hypertension may be present without glaucomatous damage to the optic disc, and only a minority of patients with ocular hypertension develop glaucoma.[1,3,4] Symptoms of glaucoma may not be apparent until it is advanced and has caused vision loss. It is estimated that at least half of all people with glaucoma are undiagnosed.[1]

There was no patient input submitted for this review. The clinical expert consulted for this review identified some important impacts of glaucoma, including the burden of living with a chronic disease and the loss of vision, which can increase a patient's risk of vehicle accidents, trips, and falls, and can lead to social deprivation and depression.

The 2008–2009 Canadian Community Health Survey on Healthy Aging estimated that 456,533 Canadians had a diagnosis of glaucoma.[16] A meta-analysis of five national surveys estimated that, from 2002 to 2003, the self-reported prevalence of glaucoma in Canada was 2.7% in those 40 years and older and 11% in those 80 years and older.[2] Some patients self-reporting glaucoma may have been receiving treatment for ocular hypertension rather than glaucoma.[3]

Standards of Therapy

The clinical practice guidelines for management of glaucoma published by the Canadian Ophthalmological Society state that lowering IOP is the only clinically established method of glaucoma treatment.[3] The guidelines recommend assigning an initial target IOP upper threshold based on the severity of glaucoma, and they outline suggestions for upper thresholds, along with minimum percentage reductions from baseline IOP.[3] The target IOP should be modified based on patient's age, life expectancy, quality of life, and risk factors for progression.[3]

Treatment strategies for reducing elevated IOP include topical or systemic medications, laser therapy, and surgery.[3] 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 ocular hypertension: prostaglandin analogues (PGAs), beta blockers, carbonic anhydrase inhibitors, alpha adrenergic agonists, and direct-acting cholinergic agonists.[3] Of these, the most common first-line therapy is PGAs, because of their favourable effectiveness, once-daily administration, and tolerability compared with the other drugs.[3] Patients who do not meet their target IOP with PGA therapy alone may receive an additional drug.[3]

Laser trabeculoplasty can be performed as an adjunct to medical therapy when target IOP is not achieved on medication alone.[3] The most common surgical procedure for glaucoma is trabeculectomy, which is employed when both medication and laser trabeculoplasty are not sufficient to achieve target IOP.[3]

Patients with OAG require lifetime therapy, but glaucoma medical therapy is often characterized by nonadherence. Possible reasons for nonadherence include the asymptomatic nature of ocular hypertension and early glaucoma, inconvenience of the medication, cost, and adverse effects (AEs).[17]

Use of topical ophthalmic solutions is associated with ocular surface disease (OSD), which can include blepharitis, Meibomian gland dysfunction, conjunctival inflammation, and keratitis.[5] Patients may experience dry eye or sensations of burning, stinging, itching, or discomfort.[5] Preservatives in topical ophthalmic solutions have been implicated in the occurrence of OSD in patients with glaucoma.[5] The most common preservative is benzalkonium chloride (BAK), which has been shown to be a risk factor for glaucoma surgery failure.[5,17] According to the clinical expert consulted for this review, the active ingredients or excipients in topical ophthalmic solutions may also contribute to OSD.

Drug

Monoprost is a preservative-free formulation of latanoprost containing 50 µg of active ingredient per millilitre (0.005%) of solution in single-use containers. The original formulation of latanoprost, Xalatan, is preserved with BAK and contains the same concentration of latanoprost. The recommended dosage of Monoprost for the reduction of IOP in patients with OAG or ocular hypertension is one drop in the affected eye(s) once daily in the evening.

The active ingredient, latanoprost, is a selective prostaglandin F (FP) prostanoid receptor agonist, which reduces IOP by increasing the outflow of aqueous humour. Its main mechanism is increased uveoscleral outflow, although some decrease in outflow resistance has also been reported.

Table 2: Key Characteristics of Prostaglandin Analogues

	Preservative-Free Latanoprost 0.005% (Monoprost), BAK-Preserved Latanoprost 0.005% (Xalatan and generics)	SofZia-Preserved Travoprost 0.004% (Travatan Z), Polyquaternium-1–Preserved Travoprost 0.003% (Izba)	BAK-Preserved Bimatoprost 0.03% (Vistitan), BAK-Preserved Bimatoprost 0.01% (Lumigan RC)
Mechanism of Action	Selective prostanoid FP receptor agonist that 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 F2 alpha. Bimatoprost exhibits no meaningful pharmacological activity at known prostaglandin receptors. Studies suggest that it lowers IOP by increasing uveoscleral and trabecular meshwork outflow.
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 underwent peripheral iridotomy or laser iridoplasty.		
Route of Administration	Topical ophthalmic solution		
Recommended Dose	One drop in the affected eye(s) once daily; optimal effect is obtained when administered in the evening		
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		
Other	There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products (not applicable to Monoprost).		

BAK = benzalkonium chloride; FP = prostaglandin F; IOP = intraocular pressure.

[a] Health Canada indication.

Source: Product monographs for Monoprost,[18] Xalatan,[19] Travatan Z,[20] Izba,[21] Vistitan,[22] and Lumigan RC.[23]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of preservative-free latanoprost 50 µg/mL ophthalmic solution (Monoprost) for the reduction of IOP in patients with OAG or ocular hypertension.

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 • Patients with versus without a history of intolerance to preserved ophthalmic solutions • Patients stratified by baseline untreated intraocular pressure • Patients stratified by baseline treated intraocular pressure
Intervention	Preservative-free latanoprost 50 µg/mL ophthalmic solution (Monoprost), one drop in the 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 (including timolol/dorzolamide, timolol/brimonidine, timolol/latanoprost, timolol/travoprost, and timolol/brinzolamide)
Outcomes	**Key efficacy outcomes:** • Intraocular pressure • Tolerability of medication using a validated scale • Adherence to medication • Health-related quality of life using a validated scale • Vision-related quality of life using a validated scale **Other efficacy outcomes:** • Visual field loss • Visual acuity • Symptoms of glaucoma • Optic nerve damage **Harms outcomes:** • AEs, SAEs, WDAEs, mortality Notable harms (conjunctival hyperemia, blepharitis, dry eye, blurred vision, photophobia, ocular pruritus, ocular irritation, excessive tearing, punctate keratitis, ocular foreign body sensation, symptoms of ocular surface disease)
Study Design	Published and unpublished phase III RCTs

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy, which is presented in Appendix 2.

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

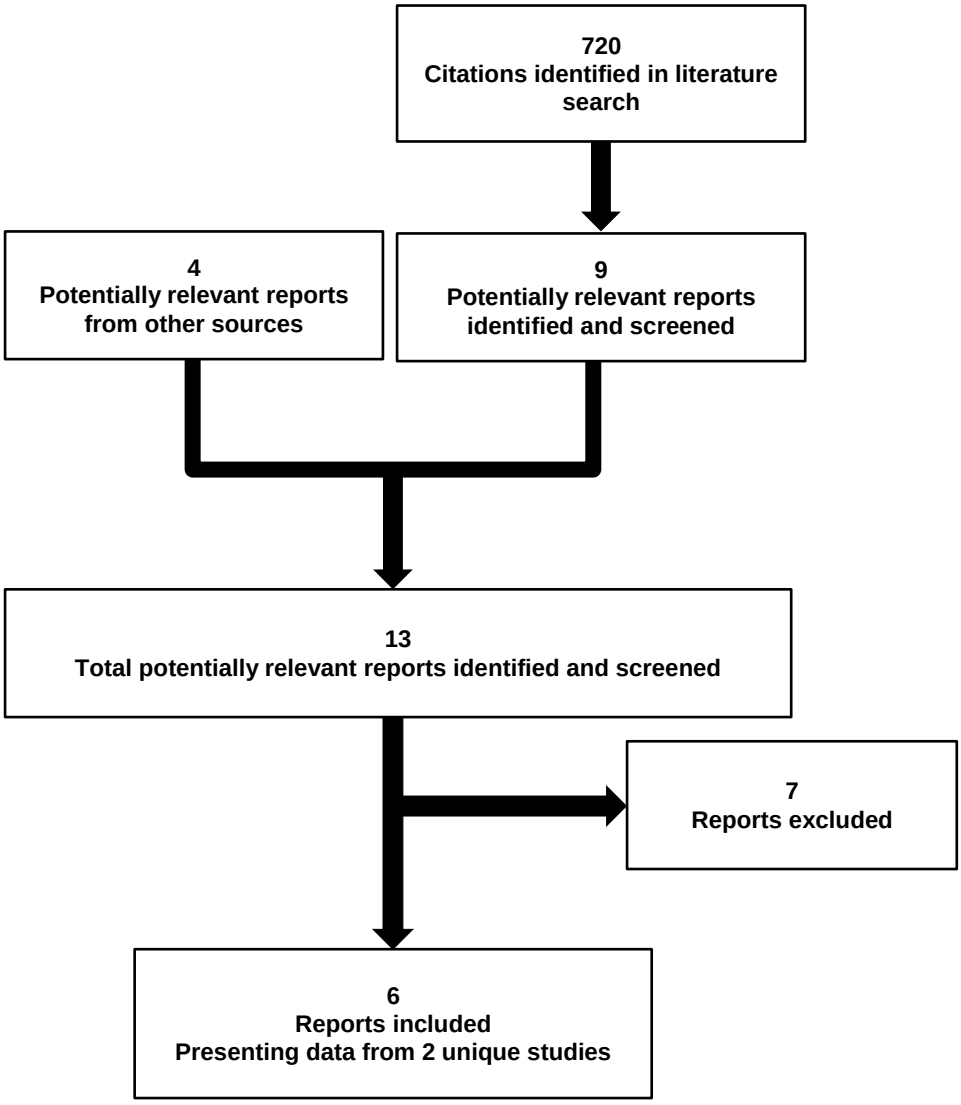


Table 4: Details of Included Studies

		Study LT2345-PIII-12/08	Study LT2345-001
Designs and Populations	**Study Design**	Phase III, investigator-masked, parallel-groups RCT	Phase III, observer-masked, parallel-groups RCT
	Locations	63 centres in Europe (including 42 centres in France) and 13 centres in Tunisia	31 centres in the US
	Randomized (N)	404	334

	Inclusion Criteria	• Age 18 to 90 years old, inclusive
		• In the eligible eye:
		  ○ Chronic primary OAG or chronic OH already treated and controlled by Xalatan monotherapy for at least 1 year (9 months in some countries) as defined by stable IOP (≤ 18 mm Hg) and stable VF
		  ○ Corneal thickness ≥ 500 µm and ≤ 580 µm
		• If both eyes were eligible, both were treated, and the one with higher IOP at baseline was the study eye (with right eye as default).
		• IOP < 34 mm Hg in both eyes and IOP ≥ 22 mm Hg in eligible eye(s) at baseline
			• Age 18 years or older
			• Primary OAG or OH with IOP controlled (≤ 18 mm Hg) with latanoprost 0.005% monotherapy for at least 4 weeks before screening
			• In the eligible eye:
			  ○ IOP ≤ 18 mm Hg at screening and ≤ 28 mm Hg at baseline
			  ○ Stable VF
			  ○ Stable corrected Snellen visual acuity better than 20/200
			  ○ Central corneal thickness 480 µm to 620 µm
			• Shaffer gonioscopic grade of ≥ 3 in at least 3 quadrants in both eyes
			• If both eyes were eligible, both were treated and the one with lower IOP at screening was the study eye (with right eye as default).

	Exclusion Criteria	In either eye: • Secondary OH • Severe glaucoma (advanced cupping and/or severe visual field loss, risk of worsening, or absolute defect in the 10° central point) • Best far corrected visual acuity ≤ 1/10 • Aphakia • Known history of ocular allergy, severe blepharitis, or uveitis • History of trauma, infection, or ocular inflammation within 3 months of screening • History of refractive surgery • Severe dry eye • Abnormality preventing accurate assessment of IOP or visual field Systemic: • Uncontrolled asthma • Known history of allergic hypersensitivity to one of the study medication components Any of the following before screening: • Filtration surgery or laser procedure for glaucoma (within 1 year) • Other intraocular surgery (within 6 months) • Systemic antiglaucoma treatments, or topical ocular steroids or NSAIDs (within 1 month) • Any predictable change in dosage regimen for systemic treatments, especially those that can substantially affect IOP (within 1 month) • Systemic immunosuppressive treatment, NSAIDs, or topical ocular treatments (within	In the study eye: • Mean deviation of < –20 dB on VF exam • A scotoma within 5° of fixation on VF exam • Aphakia • Use of antiglaucoma medication in addition to latanoprost 0.005% within 2 weeks of screening and during the study • Use of topical ophthalmic steroid or topical NSAID within 2 weeks before baseline • Use of any ophthalmic medications during the study (except for unpreserved artificial tears) • Ocular surgery or laser treatment of any kind in the study eye within 3 months of baseline • History of ocular allergy/inflammation, severe blepharitis, uveitis, or herpes simplex keratitis • History of ocular trauma or infection within 3 months of screening • Current, significant proliferative diabetic retinopathy or age-related macular degeneration • Severe dry eye • Secondary glaucoma or OH • Severe glaucoma (cup-to-disc ratio ≥ 0.8) • Contact lens wear in treated eyes during the study • Nonlaser glaucoma surgery • Abnormality preventing accurate assessment of IOP or VF Systemic: • Uncontrolled asthma • Allergy to BAK • History of moderate or severe renal or hepatic

		Study LT2345-PIII-12/08	Study LT2345-001
		15 days)	impairment
Drugs	**Intervention**	One drop q.d. of Monoprost (preservative-free latanoprost 50 µg/mL) in the eligible eye(s) once daily at 9 p.m. (± 1 hour)	One drop q.d. of Monoprost (preservative-free latanoprost 50 µg/mL) in the eligible eye(s) once daily at 8 p.m. (± 30 minutes)
	Comparator(s)	One drop q.d. of Xalatan (latanoprost 0.005% preserved) in the eligible eye(s) once daily at 9 p.m. (± 1 hour)	One drop q.d. of Xalatan (latanoprost 0.005% preserved) in the eligible eye(s) once daily at 8 p.m. (± 30 minutes)
Duration	**Phase**		
	Run-in	6 weeks from screening to baseline During run-in, brinzolamide (Azopt, a carbonic anhydrase inhibitor) was given to replace Xalatan, with a washout period of 5 days before baseline.	7 to 10 days from screening to baseline Washout period of ≥ 72 hours before baseline
	Investigator-masked treatment	12 weeks	12 weeks
	Follow-up	N/A	N/A
Outcomes	**Primary End Point**	Change from baseline to day 84 in IOP of the study eye measured with a Goldmann applanation tonometer at 9:00 a.m. (noninferiority to comparator)	IOP measured with a Goldmann applanation tonometer (equivalence to comparator) at each time of day (8:00 a.m., 10:00 a.m., and 4:00 p.m.) on each of days 15, 42, and 84
	Other End Points	Efficacy: • Change from baseline to days 15 and 42 in IOP Safety: • Ocular symptoms between instillations in each eye (all visits) • Ocular symptoms upon instillation in each eye (days 15, 42, and 84) • Global local tolerance assessed by the Investigator (days 15, 42, and 84) • Global tolerance assessed by the patient (days 14, 42, and 84) • Slit-lamp examination in each eye (all visits) • Funduscopy (cup-to-disc ratio) in each eye (screening, day 84 if necessary) • VF in each eye (screening, baseline, day 84 if necessary) • Best far corrected visual acuity in both eyes (screening, baseline, day 84) • Treatment compliance evaluation (vial counting at days 0, 42, and 84) • Ocular and systemic AEs, serious AEs	Efficacy: • Change from baseline to days 15, 42, and 84 in for study eye, at each time point and diurnally • Proportion of patients with IOP < 18 mm Hg for study eye, at each time point and diurnally Safety: • Ocular symptoms upon instillation in study eye (days 15, 42, and 84) • Global local tolerance assessed by the investigator (days 15, 42, and 84) • Slit-lamp examination in each eye at all visits (including grading of anterior chamber cells and flare) • Funduscopy (including cup-to-disc ratio) in each eye (screening and day 84) • VF in each eye (screening and day 84) • Corrected Snellen visual acuity (baseline and days 15, 42, and 84) • AEs and serious AEs
Notes	**Publications**	Rouland et al.[7]	None

AE = adverse event; BAK = benzalkonium chloride; IOP = intraocular pressure; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; OAG = open-angle glaucoma; OH = ocular hypertension; q.d. = once daily; RCT = randomized controlled trial; VF = visual field.

Note: Three additional reports were included.[24-26]

Source: Clinical Study Reports.[6,8]

Included Studies

Description of Studies

Two studies from the systematic literature search were found to be eligible. These corresponded to the phase III randomized controlled trials (RCTs) for which the manufacturer provided clinical study reports[6,8] as part of the CDR submission.[24] Both RCTs had a parallel-groups design with masking of the investigators or observers but not the patients. Both studies also compared Monoprost monotherapy with Xalatan monotherapy (branded BAK-preserved latanoprost) for efficacy in lowering IOP as well as for safety and tolerance in patients with OAG or ocular hypertension controlled by latanoprost monotherapy. LT2345-PIII-12/08[6] was a pivotal study designed to demonstrate noninferiority of Monoprost in lowering IOP to Xalatan; this study was published.[7] LT2345-001[8] was a supportive study designed to demonstrate equivalence in IOP-lowering efficacy of Monoprost and Xalatan.

Patients in the pivotal study, LT2345-PIII-12/08, were randomized using random permuted blocks with a block size of four. Patients in the supportive study, LT2345-001, were randomized using a randomized block design, although further details were not reported. In both studies, the biostatistician created the randomization list and, upon the allocation of each eligible patient at baseline, site staff assigned the patient the next available treatment number. Drug kits were numbered according to treatment number.

Patients in both studies were not blinded to treatment allocation, since Monoprost comes in a single-use format, in contrast to the multi-dose format of Xalatan. The comparator was not repackaged in single-dose containers due to potential issues with sterility and interaction between Xalatan solution and the single-dose container material.

In the pivotal study, the run-in period was six weeks, and patients were given brinzolamide, a carbonic anhydrase inhibitor, to replace their previous latanoprost therapy. There was a washout period for brinzolamide of five days before baseline. In the supportive study, the run-in period was seven to 10 days long, and patients had to discontinue their latanoprost therapy for at least 36 hours before baseline. Following the run-in period in both studies, patients were randomized to Monoprost or Xalatan therapy and followed up at 15, 42, and 84 days after baseline. In addition to IOP, investigators assessed conjunctival hyperemia, overall patient tolerance of treatment, and ocular abnormalities, while patients reported symptoms of ocular discomfort experienced upon taking the study drug. If both eyes were eligible, they were both treated with study drug. The study eye was then determined by IOP at baseline — it was the eye with the higher IOP in the pivotal study and the lower IOP in the supportive study. If both eyes had the same IOP at baseline, the right eye was the study eye. The clinical expert consulted for this review considered it unusual for the supportive study to select the eye with the lower IOP as the study eye.

Populations

Inclusion and Exclusion Criteria

Patients in both studies were adults with primary OAG or ocular hypertension controlled (i.e., IOP no greater than 18 mm Hg) for a minimum period of time with latanoprost before the study (nine months in the pivotal study and four weeks in the supportive study). By the end of the run-in period, IOP had to be below 34 mm Hg in both eyes and at least 22 mm Hg in the eligible eye(s) in the pivotal study, while IOP had to be no greater than 28 mm Hg

in the eligible eye(s) in the supportive study. There was no minimum baseline IOP specified in the protocol for the supportive study.

Patients were excluded if they had severe or secondary glaucoma, severe dry eye, aphakia, severe visual field loss, known hypersensitivity to BAK, history of ocular allergy, blepharitis, or uveitis, abnormality preventing accurate assessment of IOP, recent ocular surgery or laser treatment, or uncontrolled asthma. Patients with filtration or laser surgery for glaucoma more than a year before the pivotal study and patients with laser surgery for glaucoma more than three months before the supportive study were still potentially eligible. Corneal thickness in eligible eyes also had to be within a specified range for both studies.

Baseline Characteristics

In the pivotal LT2345-PIII-12/08 trial, study centres were located in Europe and Tunisia. The Monoprost and Xalatan groups had similar mean ages (63.7 and 65.1 years, respectively) and proportions of women (52% and 45%, respectively). IOP at screening was within 15.4 mm Hg to 15.5 mm Hg, indicating that IOP was sufficiently controlled with Xalatan. Baseline IOP following the run-in period was 24.1 mm Hg and 24.0 mm Hg, respectively, showing elevated IOP following medication washout. Summaries of medical and surgical history and ocular symptoms at screening and baseline were reported for each group in the pivotal study. There were greater proportions of patients in the Xalatan group with a history of cataracts (25% versus 20%), dry eye (9% versus 6%), and systemic hypertension (41% versus 33%), and a greater proportion of patients in the Monoprost group with hypercholesterolemia (21% versus 12%). Only a small proportion of patients had glaucoma (2% and 5% in the Monoprost and Xalatan groups), and less than 1% had OAG. According to the clinical expert consulted for this review, the low proportion of patients with glaucoma in the pivotal study may have been due to difficulty in recruiting glaucoma patients taking only one antiglaucoma medication (i.e., latanoprost). Prevalence of eye dryness sensation, irritation/burning/stinging, itching, tearing, foreign body sensation, and photophobia was similar between treatment groups, and each symptom was present in 7% or less of patients in each group.

In the supportive LT2345-001 trials, study centres were located in the US, and the Monoprost and Xalatan groups were similar in mean age (67.1 and 66.1 years, respectively) and proportions of women (63% and 60%, respectively). Most patients were white (75% and 84%, respectively) or black (23% and 15%, respectively), with some differences between treatment groups. Baseline IOP differed between the groups at the 10:00 a.m. and 4:00 p.m. time points (18.6 mm Hg and 18.4 mm Hg, respectively, for Monoprost, 19.1 mm Hg and 18.9 mm Hg, respectively, for Xalatan) and was lower than in the pivotal study, likely due to the shorter washout period (minimum of 72 hours). Most patients likely did not have glaucoma, as only 12% in the Monoprost and 19% in the Xalatan group had abnormal visual field with glaucomatous defect in the study eye at screening (see Table 15 in Appendix 4).

Table 5: Summary of Baseline Characteristics

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 189 mITT Set	**Xalatan N = 164 mITT Set**	**Monoprost N = 161 PP Set**	**Xalatan N = 164 PP Set**
Age, years, mean (SD)	63.7 (11.6)	65.1 (11.8)	67.1 (10.2)	66.1 (10.9)
Female, n (%)	99 (52)	74 (45)	102 (63)	98 (60)
Ethnicity, n (%)				
Hispanic/Latino	NR	NR	18 (11)	22 (13)
Race, n (%)				
White	NR	NR	122 (76)	138 (84)
Black	NR	NR	37 (23)	25 (15)
Asian	NR	NR	1 (0.6)	0
Other	NR	NR	1 (0.6)	1 (0.6)
Corneal thickness in study eye, µm, mean (SD)	540 (19)	540 (18)	550 (34)	548 (35)
IOP in study eye, mm Hg, mean (SD)				
Screening[a,b]	15.5 (1.8)	15.4 (1.8)	15.5 (2.0)	15.5 (1.9)
8:00 a.m.	NR	NR	15.5 (2.3)	15.6 (2.2)
10:00 a.m.	NR	NR	15.5 (2.2)	15.5 (2.4)
4:00 p.m.	NR	NR	15.4 (2.5)	15.5 (2.3)
Baseline[b]	24.1 (1.8)	24.0 (1.7)	18.8 (2.9)	19.2 (3.1)
8:00 a.m.	NR	NR	19.6 (3.3)	19.6 (3.3)
10:00 a.m.	NR	NR	18.6 (3.5)	19.1 (3.6)
4:00 p.m.	NR	NR	18.4 (2.9)	18.9 (3.5)
Selected medical and surgical history at screening				
Ocular, study eye				
Cataract	34 (18)	41 (25)	NR	NR
Hypertrichosis	35 (19)	36 (22)	NR	NR
Skin hyperpigmentation	13 (7)	7 (4)	NR	NR
Iris hyperpigmentation	12 (6)	15 (9)	NR	NR
Dry eye	9 (5)	14 (9)	NR	NR
Glaucoma	4 (2)	10 (6)	NR	NR
Open-angle glaucoma	2 (1)	0	NR	NR
Ocular surgery				
Cataract surgery	20 (11)	18 (11)	NR	NR
Iridotomy	4 (2)	2 (1)	NR	NR
Phacotrabeculectomy	2 (1)	0	NR	NR
Trabeculectomy	3 (2)	5 (3)	NR	NR
Trabeculoplasty	1 (0.5)	4 (2)	NR	NR
Systemic				
Diabetes mellitus	19 (10)	16 (10)	NR	NR
Hypercholesterolemia	39 (21)	20 (12)	NR	NR
Hypertension	63 (33)	67 (41)	NR	NR
Disturbing or very disturbing ocular symptoms at screening in study eye, n (%)	**N = 213 Safety Set**	**N = 189 Safety Set**		
Eye dryness sensation	11 (5)	5 (3)	NR	NR

	Study LT2345-PIII-12/08		Study LT2345-001	
Irritation/burning/stinging	12 (6)	11 (6)	NR	NR
Itching	7 (3)	3 (2)	NR	NR
Tearing	3 (1)	4 (2)	NR	NR
Foreign body sensation	9 (4)	6 (3)	NR	NR
Photophobia	10 (5)	11 (6)	NR	NR
Disturbing or very disturbing ocular symptoms at baseline in study eye, n (%)				
Eye dryness sensation	8 (4)	1 (1)	NR	NR
Irritation/burning/stinging	7 (3)	6 (3)	NR	NR
Itching	4 (2)	3 (2)	NR	NR
Tearing	3 (1)	1 (1)	NR	NR
Foreign body sensation	4 (2)	4 (2)	NR	NR
Photophobia	9 (4)	4 (2)	NR	NR
Total symptom score, mean (SD)[c]	0.81 (1.92)	0.66 (1.49)	NR	NR

IOP = intraocular pressure; mITT = modified intention-to-treat; NR = not reported; PP = per-protocol; SD = standard deviation.

[a] For LT2345-PIII-12/08, screening visit was 42 days before baseline; for LT2345-001, seven to 10 days before baseline.

[b] For LT2345-PIII-12/08, IOP was measured at 9:00 a.m. For LT2345-001, mean diurnal IOP was calculated from the three measurements throughout the day.

[c] Total symptom score is the sum of individual symptom scores (ordinal scale from 0 or "none" to 4 or "very disturbing"), divided by the number of symptoms present.

Source: Clinical Study Reports.[6,8]

Interventions

In the pivotal LT2345-PIII-12/08 study, Monoprost was provided in 0.3 mL single-use containers and Xalatan was provided in 5 mL multi-dose containers with 2.5 mL of solution (approximately 80 drops). During the investigator-masked treatment period from baseline to day 84, patients were instructed to instill one drop of study medication into the inferior conjunctival cul-de-sac of the pathologic eye(s) once daily at 9:00 p.m. (± 1 hour). From the screening visit to five days before baseline, patients discontinued use of latanoprost and instead used the carbonic anhydrase inhibitor brinzolamide (Azopt) in the pathologic eye(s) once every morning and evening.

In the supportive LT2345-001 study, Monoprost was provided in 0.2 mL single-use containers and Xalatan was provided in relabelled commercial multi-dose bottles. During the observer-masked treatment period from baseline to day 84, patients were instructed to administer one full drop of study medication into the eligible eye(s) once daily at 9:00 p.m. (± 30 minutes). If a full drop was not instilled, the patient had to wait 10 to 15 seconds before administering the second drop.

Investigator or observer masking was preserved by not administering the drug at the clinical site; providing both medications in identical cardboard boxes; and having separate site personnel handle, dispense, and account for the medications. In the supportive study, patients returned opened and unopened medications in the original box at each visit for accounting.

The only concomitant ocular treatment permitted in both studies was unpreserved artificial tears. In the supportive study, intranasal and inhaled systemic steroids were permitted, as well as systemic beta blockers or calcium channel blockers, provided the dosage regimen was unchanged for more than three months before screening. Short-course oral steroids were also permitted if they were completed at least two weeks before screening. In the

pivotal study, systemic treatments were permitted only if the dosage regimen was unchanged for at least one month before screening.

To evaluate treatment compliance, patients in both studies were questioned at each visit about their compliance with the treatment regimen. In the pivotal study, patients were asked about the date and time of last instillation and whether the study drug was instilled as instructed since the previous visit. If there was noncompliance, the periods with treatment modification and the number of instillations per day during these periods were solicited. The number of used and unused single-dose units and vials of returned products were counted at the baseline, and at day 42 and day 84 visits. Treatment compliance based on instillation was calculated as days of instillation since the last visit as a percentage of the days since the last visit. In the supportive study, compliance was assessed at all post-baseline visits, and patients were also asked about time of instillation and deviations from the treatment regimen. Drug accountability was performed at the end of the study. Details on patient questioning and drug accountability methods were not reported.

Outcomes

For the pivotal trial, LT2345-PIII-12/08, the primary efficacy end point was the change in IOP at 9:00 a.m. from baseline to day 84 in the study eye. Noninferiority of Monoprost to Xalatan was assessed for this end point using a margin of 1.5 mm Hg. The secondary efficacy end points were changes in IOP at 9:00 a.m. from baseline to days 15 and 42 in the worse eye. For the supportive study, LT2345-001, the primary efficacy end point was study eye IOP at 8:00 a.m., 10:00 a.m., and 4:00 p.m. on each of the day 15, 42, and 84 visits. Equivalence in IOP change from baseline of Monoprost compared with Xalatan was assessed using a margin of 1.5 mm Hg for all nine comparisons and a margin of 1.0 mm Hg for five of nine comparisons. The secondary efficacy end points were changes from baseline to days 15, 42, and 84 in study eye diurnal IOP and IOP at each time of day. The proportion of patients reaching an IOP of less than 18 mm Hg for all time points was also provided for each treatment group. The clinical expert consulted for this review indicated that a threshold of 18 mm Hg for IOP is clinically meaningful.

In the pivotal study, IOP was measured at 9:00 a.m. (± 1 hour), and two readings were averaged (three were averaged if the first two readings differed by more than 2 mm Hg) for each time point. The same investigator used the same instrument for all visits, and one drop of fluorescein-oxybuprocaine solution was administered in each eye before measuring IOP. In the supportive study, IOP was measured by the investigator, who was masked to the readout of the tonometer (which was recorded by a second staff member), and the same tonometer and investigator were used for each patient, if possible. IOP was measured at 8:00 a.m., 10:00 a.m., and 4:00 p.m. (± 30 minutes for all times, with at least two hours between morning readings) at each study visit. Diurnal IOP was calculated as the average of IOP values at the three times, provided they were all available. According to the clinical expert consulted for this review, these approaches to measuring IOP were acceptable, as IOP was measured at consistent times of the day.

IOP is closely related to glaucoma progression and is an appropriate surrogate end point for efficacy in preventing glaucoma progression. IOP was measured in both studies using Goldmann applanation tonometry, which is considered the gold standard. For more information on IOP and its measurement, see Appendix 5.

Safety and tolerability assessments were conducted in both eyes. Conjunctival hyperemia is redness in the conjunctiva — the membrane covering the front of the eye and lining the

inner surface of the eyelids — and it results from vasodilation of the conjunctival vessels. In both studies, conjunctival hyperemia was assessed by the investigator using the McMonnies photographic scale. The scale consists of photographs of the inferior conjunctiva, representing six different levels of conjunctival hyperemia covering a range of responses normally observed with contact lens use.[27,28] It has moderate inter-rater reliability,[28] strong intra-rater reliability,[28] and strong correlations with the physical and photometric properties of the reference images.[29] For further information on the McMonnies photographic scale, see Appendix 5.

Both studies asked patients at each post-baseline visit whether they had felt any unusual sensation upon instillation of the study medication (i.e., pruritus, burning/stinging, blurred vision, sticky eye sensation, eye dryness sensation, or foreign body sensation) since the previous visit. If the answer was yes, patients graded each symptom on a four-point ordinal scale ranging from 0 or "none" to 3 or "very disturbing" and provided durations for symptoms graded above 0. In the pivotal LT2345-PIII-12/08 study, a total symptom score was calculated by dividing the sum of the individual symptom scores by the number of symptoms experienced. Division by the number of symptoms experienced was not in the trial protocol or statistical analysis plan.[30,31] Patients in the pivotal study also graded symptoms experienced at least one hour before or after instillations (eye dryness sensation, foreign body sensation, irritation/burning/stinging, itching, photophobia, tearing) on the same scale and were asked whether they felt the treatment was convenient. In both studies, the investigator rated global local tolerance of the study medication on a four-point ordinal scale ranging from "very satisfactory" to "unsatisfactory." The clinical expert consulted for this review was not aware of any studies validating the total symptom score or global local tolerance assessed by the investigator as outcome measures.

In the pivotal LT2345-PIII-12/08 study, the slit-lamp examination and fluorescein test were performed at all study visits, while corrected Snellen visual acuity and visual field were assessed at screening, baseline, and day 84 (only if deemed necessary for visual field). Dilated fundus examination (with cup-to-disc ratio recorded) was performed, and corneal thickness was measured with a pachymeter at screening. Funduscopy was performed again at day 84 if IOP was not stable or if the procedure was judged necessary. Visual field was recorded as "normal/abnormal" based on use of a Humphrey field analyzer (30° or 24°) and evaluation of the mean defect or use of an Octopus analyzer. The slit-lamp examination evaluated the presence and severity of folliculo-papillary conjunctivitis, palpebral abnormality, corneal staining punctuations, anterior chamber flare, iris pigmentation modification, hypertrichosis, abnormal palpebral skin coloration, and any other ocular abnormalities.

In the supportive LT2345-001 study, the visual acuity assessment and slit-lamp examination were performed at all study visits, while visual field testing and ophthalmoscopy and dilated fundus examination were performed at screening and at day 84. Corrected Snellen visual acuity was obtained with patients' current corrective lens prescription at a distance or equivalent distance of 20 feet from the Snellen eye chart. The same refraction, obtained within six months of screening, was used for all visual acuity assessments. Visual field was tested with the 30-2 or 24-2 test using an automated perimeter, with the method used in each patient kept consistent. A routine slit-lamp examination evaluated the anterior segment of the eye, including the lids, cornea, conjunctiva, anterior chamber, iris, and lens. Anterior chamber cells were graded on a five-point ordinal scale based on the number of cells, and anterior chamber flare was graded on a similar scale with a range of "complete absence" to "intense." Direct ophthalmoscopy was

used to assess the optic nerve head for pallor and cupping, and a dilated fundus examination assessed the vitreous, optic nerve, macula, and peripheral retina. Abnormalities found on the slit-lamp and dilated fundus examinations were documented.

For both studies, ocular and systemic adverse events (AEs) were recorded at each visit, and the investigator determined the relationship of each AE to the study treatments.

Statistical Analysis

In the pivotal LT2345-PIII-12/08 study, the primary efficacy end point of mean change in IOP from baseline to day 84 was analyzed in the modified intention-to-treat (ITT) set using a mixed model for repeated measures. The model had an unstructured variance-covariance matrix and was adjusted for baseline IOP, country, visit, treatment-by-visit interaction, and baseline IOP-by-visit interaction. The 95% confidence interval (CI) for the difference in mean change between treatment groups was estimated for IOP in the study eye on days 15, 42, and 84. Monoprost was considered noninferior to Xalatan if the 95% CI was within a noninferiority margin of 1.5 mm Hg. The same analysis was also carried out in the ITT and per-protocol (PP) sets. An additional analysis was conducted with treatment-by-country and treatment-by-country-by-visit as additional factors. A sensitivity analysis was done in all three sets using the last observation carried forward (LOCF) approach with an analysis of covariance (ANCOVA) model adjusted for country and baseline IOP. This was the only imputation of data performed for the pivotal study.

All other outcomes treated as continuous variables in the pivotal study were analyzed with an ANCOVA model based on treatment, country, and baseline assessment (if available). Dichotomous and ordinal outcomes (including global assessment of efficacy, subjective ocular signs, global assessment of tolerance, and conjunctival hyperemia severity) were analyzed using the Cochran–Mantel–Haenszel test stratified by country. Modified ridit scores were used for ordinal outcomes. Aside from IOP analyses, all statistical tests for the comparison between treatment groups were two-sided, with a 5% significance level. No adjustments were made for multiple testing.

Sample size was based on the noninferiority margin and assumed slightly worse efficacy of Monoprost (mean difference of 0.5 mm Hg) and a standard deviation of 3.0 mm Hg in the primary efficacy end point. A sample size of 180 evaluable patients in each group was expected to provide 88% power to demonstrate noninferiority of Monoprost.

In the LT2345-001 supportive study, several amendments were made to the statistical analysis plan two years after the original plan had been finalized. According to the report, “A revision of the SAP [statistical analysis plan] was deemed relevant to ensure consistency of reporting to Competent Authorities of outcomes stated in other studies conducted with the same investigational product after database lock.”[32]

In the original plan, descriptive statistics were planned to be presented for the primary efficacy end point, IOP of the study eye at each time on each of the post-baseline visit days for the PP set. The equivalence margin was set as 1.5 mm Hg, meaning that the limits of the 95% CI of the difference in IOP between the treatment groups had to be within –1.5 mm Hg to 1.5 mm Hg. Additionally, the majority of the nine measurements of mean difference in IOP had to be within 1.0 mm Hg. These criteria were in alignment with the FDA’s definition for establishing equivalency.[33] However, the difference between treatment groups in change in IOP from baseline was used in the main efficacy analysis in the report. Analyses

of IOP in the contralateral eye were added as part of the amendments to the statistical analysis plan.

Diurnal IOP in the study eye at each post-baseline visit was originally planned to be compared between the treatment groups using an unadjusted ANCOVA model. The ANCOVA model was later amended to control for study site (sites were pooled if they had fewer than 10 patients enrolled) and baseline IOP. The amendments also added analyses of change in diurnal IOP from baseline and from screening (controlled for screening IOP instead of baseline IOP). Similar analyses of change in IOP at each time of day from baseline and from screening were also added.

The amended statistical analysis plan also added ANCOVA analysis for conjunctival hyperemia, as assessed by the investigator on the McMonnies scale, controlling for study site and baseline score. Comparisons of mean score between treatment groups were tested at a 5% significance level, and no adjustments were made for multiple testing. While the main efficacy analyses were done in the PP set, additional analyses in the ITT set were performed for observed values only and for all values including missing values imputed using the LOCF approach (another amendment).

Sample size was based on an equivalence limit of 1.5 mm Hg and an estimated standard deviation of 3.0 mm Hg. A sample size of 86 subjects in each group was expected to provide 90% power to demonstrate equivalence with Monoprost. The original protocol[34] was based on the sample-size calculations for the pivotal study and was subsequently revised to match the number of patients recruited at the time (approximately 165 patients per group).

Analysis Populations

In both studies, the safety set comprised all enrolled patients who used the study medication, and patients were assigned to groups according to the treatment they actually received. In the pivotal study, the safety set included only patients with any follow-up data.

In the pivotal study, the ITT set included all randomized patients for whom any follow-up IOP data were available for the study eye. The modified ITT set, used for the primary efficacy analysis, consisted of ITT patients who received at least one dose of study medication. Patients were excluded from the modified ITT set if they had at least one major protocol deviation in both eyes, although this was not specified in the protocol.[30] Patients were assigned as randomized in the ITT set, whereas patients were assigned as treated in the modified ITT set. The PP set was a subset of the modified ITT set that included only patients without a major protocol violation, potentially influencing both the day 42 and 84 IOP measurements. Also, efficacy data (IOP and global assessment of efficacy by the investigator) were excluded for any visit with a protocol violation influencing the IOP measurement.

In the supportive study, the ITT set included all randomized subjects who had evidence of receiving at least one dose of study medication. Patients were assigned as randomized, and only observed data were used for efficacy analyses. The PP set, which was used for the primary efficacy analysis, consisted of ITT patients who had no major protocol deviations and no missing data (98% and 96% of the ITT set).

Patient Disposition

The percentage of patients discontinuing the study was 3% or less of those randomized in both treatment arms in both studies. However, only 86% to 88% of patients in the LT2345-PIII-12/08 pivotal study received at least one dose of study medication and had at least one follow-up IOP measurement (modified ITT set). In the LT2345-001 supportive study, the PP set — patients who received at least one dose of study medication and had no major protocol deviations and no missing data — consisted of 96% to 98% of randomized patients.

There were large numbers of actual or potential protocol deviations in both studies. Most major protocol deviations in the pivotal study were related to the inclusion criteria of minimum baseline IOP and corneal thickness range in the pivotal study (30% to 31% of patients). Only 36 out of 82 patients in the Monoprost group and 36 out of 71 patients in the Xalatan group with major protocol deviations were excluded from the PP set in the pivotal study.

Most protocol deviations in the supportive study were related to noncompliance with study drug, and the difference between the treatment groups was large (70% and 19% of patients in the Monoprost and Xalatan groups, respectively). It was not possible to assess, using the collected data, whether these patients met the definition for a major protocol deviation (missing at least 48 hours of consecutive treatments), and these patients were retained in the PP set used for efficacy analyses. For significant proportions of patients in the Monoprost (24% and 20%) and Xalatan (25% and 24%) groups in the ITT set, visit windows were not in range and visit procedures were not followed. Only 2% and 4% of patients in the Monoprost and Xalatan ITT groups were excluded from the PP set.

Table 6: Patient Disposition

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost	**Xalatan**	**Monoprost**	**Xalatan**
Screened, N	463		NR	
Randomized, N	214	190	165	170
Discontinued, n (%)[a]	7 (3)	3 (2)	3 (2)	4 (2)
Adverse event	3 (1)	1 (0.5)	1 (0.6)	1 (0.6)
IOP < 22 mm Hg at baseline	2 (0.9)	1 (0.5)	N/A	N/A
Lost to follow-up	1 (0.5)	0	1 (0.6)	0
Withdrew consent	1 (0.5)	0	0	3 (2)
Use of commercial Xalatan	0	1 (0.5)	0	0
Other	0	0	1 (0.6)	0
ITT, N (%)	210 (98)[b]	189 (99)[b]	164 (99)[c]	170 (100)[c]
mITT, N (%)	189 (88)[d]	164 (86)[d]	N/A	N/A
PP, N (%)	177 (83)[e]	153 (81)[e]	161 (98)[f]	164 (96)[f]
Safety, N (%)	213 (100)	189 (99)	165 (100)	169 (99)

IOP = intraocular pressure; ITT = intention-to-treat; mITT = modified intention-to-treat; N/A = not applicable; NR = not reported; PP = per-protocol.

[a] Values for the LT2345-PIII-12/08 study were provided for the safety set and values for LT2345-001 study were provided for the ITT set.

[b] Randomized patients with any follow-up data in the study eye.

[c] Randomized patients who received at least one dose of study drug.

[d] Randomized patients who received at least one dose of study drug and had any follow-up data in the study eye. Patients were excluded if they had at least one major protocol deviation in both eyes.

[e] mITT patients with major protocol deviations potentially influencing day 42 or 84 measurements.

[f] ITT patients with no major protocol deviations and no missing data.

Source: Clinical Study Reports.[6,8]

Table 7: Protocol Deviations

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 214 Randomized	**Xalatan N = 190 Randomized**	**Monoprost N = 164 ITT Set**	**Xalatan N = 170 ITT Set**
Number of major protocol deviations	136	111	NR	NR
Patients with at least one major protocol deviation, n (%)	82 (38)	71 (37)	132 (81)[a]	91 (54)[a]
Treatment duration < 70 days	4 (2)	2 (1)	NR	NR
Blinding procedure not followed	8 (4)	6 (3)	NR	NR
Noncompliance with washout period	1 (1)	2 (1)	NR	NR
Noncompliance with study drug[b]	7 (3)	3 (2)	114 (70)	32 (19)
Primary efficacy data (IOP measurement not in time range or missing)	7 (3)	11 (6)	NR	NR
Visit windows not in range	NR	NR	39 (24)	43 (25)
Visit procedures not followed	NR	NR	32 (20)	41 (24)
Concomitant medications	NR	NR	1 (1)	1 (1)
Randomization	NR	NR	0	1 (1)
Inclusion criteria not met	66 (31)	57 (30)	1 (1)[c]	5 (3)[c]
Mean IOP < 22 mm Hg in	35 (16)	19 (10)	NR	NR

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 214 Randomized	Xalatan N = 190 Randomized	Monoprost N = 164 ITT Set	Xalatan N = 170 ITT Set
eligible (right) eye at baseline				
Mean IOP < 22 mm Hg in eligible (left) eye at baseline	37 (17)	30 (16)	NR	NR
Corneal thickness not within range of 500 µm to 580 µm	18 (8)	17 (9)	NR	NR
Number of patients excluded from analysis sets, n (% of larger set)				
Excluded from safety set (lack of follow-up IOP data)	3 (1)	0	N/A	N/A
ITT patients excluded from mITT set (due to major protocol deviation)	21 (10)	25 (13)	N/A	N/A
mITT patients excluded from PP set (due to major protocol deviation)	12 (6)	11 (7)	N/A	N/A

ITT = intention-to-treat; mITT = modified intention-to-treat; N/A = not applicable; NR = not reported; IOP = intraocular pressure; ITT = intention-to-treat.

[a] Protocol deviation — not necessarily a major protocol deviation.

[b] For LT2345-PIII-12/08, noncompliance with study drug was defined as ≥ 36 hours between last instillation and IOP measurement, or compliance of < 70%. For LT2345-001, noncompliance with study drug defined as missing ≥ 48 hours of consecutive treatments. In L2345-001, compliance was based on accounting of returned drug and duration of noncompliance could not be verified.

[c] Inclusion or exclusion criteria not followed.

Source: Clinical Study Reports.[6,8]

Treatment Compliance and Exposure to Study Treatments

Based on patient questioning about treatment and time of instillation, the percentage of patients compliant with study medication in the pivotal study ranged from 78% to 96% (Table 8). At the day 42 and 84 visits, compliance with study medication was lower in the Monoprost group (78% and 82%) compared with the Xalatan group (93% and 91%). Mean compliance based on days with drug instillation was similar between the groups (ranging from 98.4% to 99.7%). All of the patients reporting less than 70% compliance based on amount of instillations were in the Monoprost group (n = 6), and compliance ranged from 50% to 65% between visits in these patients. Of the six patients with less than 70% compliance, two were excluded from the modified ITT set, and two more were excluded from the PP set.

The supportive study showed a much higher percentage of patients in the Monoprost group with a deviation from the proposed study medication dose regimen (70%) than in the Xalatan group (19%), based on counting returned study-drug containers. Since duration of noncompliance was not available, and noncompliance was defined as a patient missing at least 48 hours of consecutive treatments, these patients were not considered to have had a compliance-related major protocol deviation.

Similar washout periods were followed in both groups in the supportive study. A recalculation of the mean washout period excluding an outlying patient in the Monoprost group yields a mean value of 6.3 days, which is identical to the value in the Xalatan group.

Table 8: Treatment Compliance and Exposure in the Safety Set

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 213 Safety Set	**Xalatan N = 189 Safety Set**	**Monoprost N = 164 Safety Set**	**Xalatan N = 167 Safety Set**
Patients compliant with protocol, n (% of those responding)				
Day 15	200 (96)	174 (91)	NR	NR
Day 42	164 (78)	174 (93)	NR	NR
Day 84	172 (82)	171 (91)	NR	NR
Compliance with protocol based on amount of drug instilled, % of protocol, mean (range)				
Baseline to day 42	99.1 (54.8 to 102.6)[a]	99.3 (71.4 to 104.8)	NR	NR
Day 42 to day 84	98.4 (50.0 to 100.0)	99.7 (81.8 to 102.4)	NR	NR
Patients with < 70% compliance, n (%)	6 (3)	0	NR	NR
Treatment duration, days, mean (SD)	82.5 (12.5)	83.4 (9.3)	82.5 (6.5)	82.6 (4.7)
Treatment duration, days, range	8 to 106	11 to 105	16 to 98	56 to 91
Patients exposed, n (%)				
1 to < 4 weeks	NR	NR	1 (0.6)	0
8 to < 13 weeks	NR	NR	156 (95)	163 (98)
≥ 13 weeks	NR	NR	7 (4)	4 (2)
Washout period, days, mean (SD)	NR	NR	8.5 (28.6)[b]	6.3 (3.2)

NR = not reported; SD = standard deviation.

Note: Summaries of compliance are based on patient questioning and not drug accountability.

[a] Excludes one patient who had compliance of 300% and was withdrawn from the study.

[b] Includes one patient with a washout period of 372 days.

Source: Clinical Study Reports.[6,8]

Critical Appraisal

Internal Validity

Both studies were randomized, with random permuted blocks used in the pivotal LT2345-PIII-12/08 study. The LT2345-001 supportive study used a randomized block design, although further details were not reported. Since drug kits were provided in identical boxes and were distributed based on the treatment number assigned from the randomization list, the risk of bias from randomization and allocation concealment (from the investigator) was low.

Patients were not blinded to treatment assignment because of difficulties in repackaging the comparator drug into single-dose units. According to the clinical expert consulted for this review, this situation is common in studies comparing ophthalmologic drugs. This lack of blinding is a potential source of bias for the grading of ocular symptoms, assessment of treatment convenience, and patient reporting of treatment compliance and AEs. Some patients in the Monoprost group may have expected to experience less ocular symptoms compared with their previous Xalatan treatment and may have underreported symptoms and their severity as a result.

Investigators were blinded to treatment and performed assessments of IOP, global efficacy, conjunctival hyperemia, and ocular abnormalities. Risk of bias for IOP and conjunctival hyperemia was further minimized by having a second observer record the IOP readout (in the supportive study) and by using a photographic scale to assess conjunctival hyperemia.

Most baseline characteristics were balanced between groups in both studies, although there were some exceptions. There was a greater proportion of women in the Monoprost group than in the Xalatan group in the pivotal study, and there were differences in proportions of those identifying as white and black in the supportive study. However, the clinical expert consulted for this review was not aware of evidence that these would have been prognostic factors for the outcomes in the studies.

In the supportive study, baseline IOP was 0.5 mm Hg higher at two times of the day in the Xalatan group compared with the Monoprost group. There was potential for residual effects from pre-study Xalatan therapy on baseline IOP, as the mean washout period was 6.3 days and the FDA-recommended minimum washout period for PGAs is four weeks.[35] It is unclear how this may have affected baseline IOP as well as measurements of change in IOP from baseline to subsequent visits.

In the pivotal study, 31% and 30% of patients in the Monoprost and Xalatan groups did not meet the inclusion criteria. It is unclear from the clinical study report why the protocol was not strictly followed. Only patients with a major protocol deviation in both eyes were excluded from the modified ITT set, and this made up less than half of the patients who failed to meet the inclusion criteria. This approach was not pre-specified in the study protocol; rather, the exclusion of patients from the various analysis sets was done during a blind review of the data before database lock. A rationale was not given for the approach, and it is not clear what bias, if any, was introduced. In addition, not all patients who failed to meet the inclusion criteria were excluded from the PP set.

The proportion of patients who discontinued the study was less than 4% in each treatment group, and the proportions of patients excluded from each analysis set were balanced between treatment groups. Therefore, the risk of bias from attrition is low.

In the pivotal study, the statistical analysis plan was finalized two days after the blind review meeting, and the clinical study report followed the pre-specified analyses, where data were available. In the supportive study, the statistical analysis plan was amended following database lock. Many changes were made, including changes to the primary efficacy end point. The study protocol indicated that mean IOP values would be compared between treatment groups for each measurement, and this was changed to analysis of mean IOP change from baseline using an ANCOVA model adjusted for baseline IOP and study site.[32,34] Although patient adherence to or compliance with treatment is an important outcome for demonstrating the potential benefits of Monoprost compared with Xalatan, treatment compliance was inadequately measured in both studies. Duration of noncompliance, essential for determining the importance of episodes of noncompliance, was not reported in the supportive study. Reporting of compliance depended upon recall of patients during questioning in the pivotal study and counting of returned drug containers in the supportive study. Patient reporting of compliance may have been biased due to lack of blinding, and the amount of returned Xalatan in each bottle was not measured. The latter issue was apparent in the large difference in proportions of noncompliant patients in the supportive study (70% versus 19% in the Monoprost and Xalatan groups, respectively). The decision not to exclude noncompliant patients could have biased the supportive study IOP results in either direction, depending on which group had more treatment compliance. The

group with more treatment compliance could not be determined with certainty, owing to limitations in the measurement of compliance.

The McMonnies photographic scale, originally developed for measuring response to contact lenses, was used to assess conjunctival hyperemia. Information on the responsiveness of the scale and minimal clinically important difference (MCID) were not found. Severity of conjunctival hyperemia in a patient may not correspond to that patient's ability to tolerate or adhere to the medication. According to the clinical expert consulted for this review, one patient may be more bothered by a given level of severity of conjunctival hyperemia than another patient.

Ocular symptoms during and between instillations were not assessed using a validated scale. While the individual scale response levels may be clinically meaningful, the psychometric properties of the total symptom score are unknown. The comparison between treatments for the distribution of responses over multiple study visits is also difficult to interpret.

Both studies based their sample-size calculations on the primary efficacy outcomes to demonstrate equivalence and noninferiority of Monoprost with Xalatan. The sample size in the supportive study was revised in the protocol to match the number of patients already recruited. The revised sample size estimate did not take into account the 1.0 mm Hg margin that needed to be met by the majority of the IOP measurements. Therefore, the supportive study may not have had enough power to fully demonstrate equivalence of Monoprost with Xalatan. No consideration in terms of sample size was made for any of the tolerability or safety outcomes.

The primary efficacy analysis in the pivotal study used the modified ITT set, although the PP set is preferable for the main analysis when assessing noninferiority. Also, the PP sets in both studies were not true PP sets, since not all patients with protocol deviations were excluded.

None of the end points were adjusted for multiple comparisons, and statistical analyses outside of the primary efficacy analyses should be considered exploratory. While missing data were appropriately dealt with for the IOP end points using sensitivity analyses, missing data were not taken into account for the tolerability outcomes.

External Validity

The studies were designed to demonstrate noninferior and equivalent efficacy in lowering IOP of Monoprost compared with Xalatan. Latanoprost is indicated for the reduction of IOP in patients with OAG or ocular hypertension. According to medical history at screening, almost all of the patients in the pivotal study were being treated for ocular hypertension, rather than OAG. In the supportive study, 12% to 19% of patients had abnormal visual field with glaucomatous defect in the study eye, although summaries of medical history were not reported. According to the clinical expert, there may have been difficulty in finding patients with OAG on monotherapy, and differences in efficacy and tolerability were not expected between the two groups of patients. Patients in the supportive study represented a larger range of controlled IOP at screening (8.0 mm Hg to 22.0 mm Hg at 8:00 a.m.) compared with the pivotal study (10.0 mm Hg to 18.0 mm Hg at 9:00 a.m.), which had a minimum baseline IOP. Information on disease duration and previous antiglaucoma medications was not reported in the studies.

The studies were conducted in Europe, Tunisia, and the US. Limited information on the study demographics were available, although the clinical expert did not have any concerns about the age and gender characteristics and was not aware of any evidence that race or ethnicity is a predictor of treatment efficacy.

The clinical expert indicated that the selection criteria for the studies were reasonable, although the possibility of including patients with a history of filtration or laser surgery for glaucoma may have been unusual. Patients who had these procedures were found only in small numbers in the pivotal study. Patients were required to have their IOP controlled on Xalatan monotherapy for a minimum period of time (four to 12 months) before the studies. Therefore, the studied population was one in which latanoprost had already demonstrated efficacy.

The treatment regimens followed the respective product monographs, and the comparator was appropriate, given that BAK-preserved latanoprost is a PGA used in Canada for lowering IOP. According to the clinical expert, the follow-up time of three months was sufficiently long to compare IOP-lowering efficacy and tolerability of the treatments. Outcome measures related to changes in visual field and other symptoms of glaucoma require a much longer follow-up period and were outside the scope of the studies.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported below. See Appendix 4 for detailed efficacy data.

Intraocular Pressure

In study LT2345 PIII-12/08, the 95% CI for the difference between treatment groups in mean change in IOP from baseline to day 84 at 9:00 a.m. was within the pre-specified 1.5 mm Hg noninferiority margin (mean 0.42 mm Hg; 95% CI, 0.00 mm Hg to 0.84 mm Hg; Table 9). The same results were found at days 15 and 42. When missing data were imputed using the LOCF approach, the primary efficacy end point still demonstrated noninferiority (mean 0.40 mm Hg; 95% CI, –0.02 mm Hg to 0.83 mm Hg). The same analyses in the ITT and PP sets yielded consistent results that demonstrated noninferiority. Using the mixed-effects model, the difference for the ITT set was 0.44 mm Hg (95% CI, 0.02 mm Hg to 0.086 mm Hg), and the difference for the PP set was 0.41 mm Hg (95% CI, –0.03 mm Hg to 0.85 mm Hg). Noninferiority was similarly demonstrated using the LOCF approach in the ITT and PP sets.

In study LT2345-001, the 95% CI for the difference between treatment groups in mean change of IOP from baseline to each of days 15, 42, and 84 at all three times of day fell within a 1.5 mm Hg margin, and the first pre-specified criterion for equivalence was met. However, only four of the nine 95% CIs met the 1.0 mm Hg margin, and the second criterion for equivalence was not met in the main analysis. Additional analyses in the ITT population with and without the LOCF approach yielded similar results.

In the contralateral eye (i.e., the eye with the higher IOP at baseline) in the supportive study, both equivalence criteria were met, with five out of nine 95% CIs meeting the 1.0 mm Hg margin in the PP population as well as in the ITT population, with and without the LOCF approach. In the four measurements exceeding the 1.0 mm Hg margin in the PP population, the upper bounds of 95% CIs ranged from 1.07 mm Hg to 1.34 mm Hg, while the lower bounds ranged from 0.04 to 0.26 mm Hg. IOP measurements in the contralateral

eye were not available for four patients in the Monoprost group and six patients in the Xalatan group.

The supportive study also analyzed proportions of patients achieving a study eye IOP of less than 18 mm Hg for each measurement, although statistical testing was not performed. Diurnal IOP was below 18 mm Hg at day 84 for 73% of patients in the Monoprost group and 79% of patients in the Xalatan group. The percentage of responders was consistently lower in the Monoprost group than in the Xalatan group for all times of day at all post-baseline visits.

In both studies, mean IOP was consistently lower in the Xalatan group for all post-baseline measurements (Table 9 and Table 12 in Appendix 4). In the supportive study, this trend persisted despite the higher mean IOP at baseline for the Xalatan group. IOP measurements were missing for five patients or less at each visit, for both groups in both studies. Results for additional efficacy outcomes are provided in Table 13 in Appendix 4. Cup-to-disc ratio was similar between the treatment groups in both studies. In the pivotal study, there were more patients with an abnormal visual field with glaucomatous defect in the Xalatan group than in the Monoprost group at both baseline and day 84 (18% and 19% for Xalatan versus 12% and 13% for Monoprost). Visual field did not change from screening to baseline in either groups (–1.2 to –1.4 for Monoprost; –1.6 to –1.7 for Xalatan).

Table 9: Key Efficacy Outcomes

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 189 mITT Set	**Xalatan N = 164 mITT Set**	**Monoprost N = 161 PP Set**	**Xalatan N = 164 PP Set**
Study eye IOP at 9:00 a.m., mm Hg, mean (SD)				
Baseline	24.1 (1.8)	24.0 (1.7)	NR	NR
Day 84 (primary efficacy end point)	15.4 (2.3)	15.0 (2.0)	NR	NR
Change from baseline, mean (95% CI)	–8.6 (–9.0 to –8.3)	–9.0 (–9.4 to –8.7)	NR	NR
Difference in change, Monoprost versus Xalatan, mean (95% CI)[a]	0.42 (0.00 to 0.84) Noninferiority margin of ± 1.5 mm Hg met		NR	NR
Day 15 (secondary efficacy end point)	15.8 (2.6)	15.2 (2.4)	NR	NR
Change from baseline, mean (95% CI)	–8.3 (–8.7 to –7.9)	–8.8 (–9.2 to –8.4)	NR	NR
Difference in change, Monoprost versus Xalatan, mean (95% CI)[a]	0.57 (0.08 to 1.06)		NR	NR
Day 42 (secondary efficacy end point)	15.3 (2.3)	15.0 (2.1)	NR	NR
Change from baseline, mean (95% CI)	–8.8 (–9.2 to –8.4)	–9.0 (–9.4 to –8.6)	NR	NR
Difference in change, Monoprost versus Xalatan, mean (95% CI)[a]	0.27 (–0.16 to 0.71)		NR	NR
Change in study eye IOP from baseline, mm Hg, mean (SD); Difference in change in study eye IOP from baseline, Monoprost versus Xalatan, mm Hg, mean (95% CI)[b]				
Day 15				
8:00 a.m.	NR		–3.0 (3.2)	–3.8 (3.4)
			0.78 (0.20 to 1.37)	
10:00 a.m.	NR		–2.7 (2.9)	–3.6 (3.3)

	Study LT2345-PIII-12/08		Study LT2345-001	
			0.66 (0.16 to 1.17)	
4:00 p.m.	NR		–2.3 (2.8)	–3.1 (3.3)
			0.54 (0.03 to 1.06)	
Day 42				
8:00 a.m.	NR		–3.0 (3.2)	–3.5 (3.2)
			0.48 (–0.09 to 1.05)	
10:00 a.m.	NR		–2.7 (3.1)	–3.5 (3.4)
			0.51 (–0.01 to 1.02)	
4:00 p.m.	NR		–2.3 (2.9)	–3.1 (3.4)
			0.54 (0.00 to 1.07)	
Day 84				
8:00 a.m.	NR		–3.0 (3.3)	–3.8 (3.1)
			0.81 (0.29 to 1.33)	
10:00 a.m.	NR		–2.7 (3.0)	–3.6 (3.1)
			0.63 (0.14 to 1.11)	
4:00 p.m.	NR		–2.2 (2.8)	–2.9 (3.2)
			0.46 (–0.06 to 0.98)	
Patients with study eye IOP < 18 mm Hg, n (%)				
Day 15				
8:00 a.m.	NR	NR	97 (60)	120 (73)
10:00 a.m.	NR	NR	112 (70)	116 (71)
4:00 p.m.	NR	NR	110 (68)	113 (69)
Day 42				
8:00 a.m.	NR	NR	103 (64)	112 (68)
10:00 a.m.	NR	NR	114 (71)	125 (76)
4:00 p.m.	NR	NR	104 (65)	117 (72)
Day 84				
8:00 a.m.	NR	NR	106 (66)	114 (70)
10:00 a.m.	NR	NR	110 (68)	126 (77)
4:00 p.m.	NR	NR	109 (68)	115 (70)

CI = confidence interval; IOP = intraocular pressure; mITT = modified intention-to-treat; NR = not reported; PP = per-protocol; SD = standard deviation.

Note: If both eyes were eligible, study eye was the eye with higher baseline IOP in LT2345-PIII-12/08 and the eye with lower baseline IOP in LT2345-001. If both eyes had the same baseline IOP, the right eye was the study eye.

[a] Mixed-effects model for repeated measures adjusted for baseline IOP, country, visit, treatment-by-visit interaction, and baseline IOP-by-visit interaction.

[b] Analysis of covariance on change from baseline adjusted for pooled site and baseline IOP.

Source: Clinical Study Reports.[6,8]

Tolerability

Tolerability outcomes were measured in the safety set for both studies.

In the pivotal study, most patients (about 75%) had the lowest score of 1 on the McMonnies scale for conjunctival hyperemia, corresponding to absence of hyperemia (Table 10). There were no patients with a score of 5 or 6 at any of the post-baseline visits. At baseline, the score distributions were similar between the Monoprost and Xalatan groups. Following baseline, there was a consistent difference in score distributions in favour of Monoprost, which was most pronounced at days 42 and 84 (*P* values of 0.003 and 0.019, respectively). Absolute differences between groups in each category ranged from 1% to 7%.

In the supportive study, mean McMonnies scale score was compared between groups, and differences were not found at any of the study visits. Mean scores in each group and at each time point ranged from 1.7 to 1.9.

At each post-baseline visit in the pivotal study, ocular symptoms upon instillation reported by patients were rated as “disturbing” or “very disturbing” in less than 4% of patients in each treatment group. Score distributions were compared between treatment groups, and the only symptoms with *P* values of 0.05 or less were pruritus at day 42 and burning/stinging at days 15, 42, and 84. While consistently higher percentages of patients had “disturbing” and “very disturbing” burning/stinging (*P* values of 0.006 and less for the score distributions at each visit), the greatest differences were in the “present not disturbing” category (absolute differences of 3.9% to 5.6% of patients). The *P* value for pruritus at day 42 was 0.02, although there were less than 4% of patients in each category other than “none.” At each post-baseline visit in the supportive study, less than 2% of patients in each treatment group reported “disturbing” or “very disturbing” for each ocular symptom upon instillation.

In the pivotal study, irritation/burning/stinging was the only symptom between instillations with a *P* value of less than 0.05 (ranging from 0.04 to 0.05), and the largest absolute difference between treatment groups in the proportion of patients with the symptom was in the “present not disturbing” category. The total symptom score, the mean score of present symptoms, was higher in the Xalatan group for symptoms both upon and between instillations for all post-baseline visits. *P* values for the comparisons were less than 0.05 at days 42 and 84. Total symptom scores at all time points were less than 1, and differences between the treatment groups ranged from 0.13 to 0.28. Baseline total symptom score for ocular symptoms between instillations was higher in the Monoprost group (0.81 versus 0.66).

In both studies, investigator’s global assessment of local tolerance was graded on a four-point ordinal scale from “unsatisfactory” to “very satisfactory,” and the proportion of patients assigned a grade of “unsatisfactory” or “not very satisfactory” was less than 3% in both groups over all time points and was similar between the groups (Table 14 in Appendix 4). Differences in score distributions between the groups were associated with *P* values of less than 0.05 at days 42 and 84 (0.013 and 0.047, respectively). The main differences were in the “satisfactory” and “very satisfactory” categories, with the Xalatan group having more patients in the “satisfactory” category and fewer patients in the “very satisfactory” category.

The percentage of patients who felt treatment was convenient was higher than 96% in both treatment groups at all time points (Table 14 in Appendix 4). A higher proportion of patients in the Monoprost group felt treatment was convenient at day 84 (*P* = 0.016).

Data for tolerability outcomes were missing for seven patients or less at each visit for both groups in both studies.

Results for safety outcomes are provided in Table 15 in Appendix 4. in the pivotal study, differences in the distributions of severity of ocular signs and abnormalities were not statistically significant. In the supportive study, *P* values were not provided, although the percentages of patients with clinically significant abnormalities were less than 2% for all time points, with the exception of lens abnormalities (less than 5% for all time points). Change in visual acuity was not clinically meaningful, according to the clinical expert.

Table 10: Key Tolerability Outcomes

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 213 Safety Set	**Xalatan N = 189 Safety Set**	**Monoprost N = 165 Safety Set**	**Xalatan N = 169 Safety Set**
Investigator's assessment of conjunctival hyperemia (McMonnies photographic scale) in the study eye, % of patients, score = 2 / 3 to 4 / 5 to 6, *P* value[a]				
Screening[b]	26 / 8 / 0.5	24 / 10 / 0.5	NR	NR
Baseline	17 / 7 / 0.5	20 / 3 / 0	NR	NR
Day 15	20 / 7 / 0	27 / 6 / 0	NR	NR
	P = 0.18			NR
Day 42	15 / 5 / 0	22 / 9 / 0	NR	NR
	P = 0.003			
Day 84	17 / 5 / 0	22 / 8 / 0	NR	NR
	P = 0.019			
Investigator's assessment of conjunctival hyperemia (McMonnies photographic scale) in the study eye, mean (SD)				
Screening[b]	NR	NR	1.9 (1.1)	1.9 (1.1)
Baseline	NR	NR	1.7 (1.0)	1.7 (1.0)
Day 15	NR	NR	1.9 (1.1)	1.8 (1.1)
Day 42	NR	NR	1.9 (1.2)	1.8 (1.0)
Day 84	NR	NR	1.9 (1.1)	1.8 (1.0)
Change from baseline, LSM difference, Monoprost versus Xalatan, *P* value[c]				
Day 15	NR	NR	–0.010, *P* = 0.90	Reference
Day 42	NR	NR	0.061, *P* = 0.50	Reference
Day 84	NR	NR	–0.061, *P* = 0.49	Reference
Disturbing or very disturbing ocular symptoms upon instillation, % of patients, day 15 / day 42 / day 84, *P* value[a]				
Pruritus	1.5 / 0.5 / 0	1.1 / 2.2 / 2.2	0 / 1.2 / 1.9	0 / 0.6 / 0
	P = 0.69 / 0.02 / 0.10		NR	
Burning/stinging	1.4 / 1.0 / 0.5	3.2 / 2.7 / 3.2	0 / 0 / 0.6	1.2 / 1.2 / 0.6
	P = 0.004 / 0.006 / < 0.001		NR	
Blurred vision	0 / 0.5 / 0.5	1.6 / 1.6 / 2.7	0.6 / 1.2 / 1.2	0.6 / 0 / 0
	P = 0.56 / 0.10 / 0.24		NR	
Sticky eye sensation	0 / 0 / 0	0 / 0 / 0	0 / 0 / 0	0 / 0 / 0
	P = 0.41 / 0.62 / 0.77		NR	
Eye dryness sensation	0.5 / 0 / 0	0 / 0 / 0	0 / 0 / 1.2	0 / 0.6 / 0

	Study LT2345-PIII-12/08		Study LT2345-001	
	P = 0.92 / 0.07 / 0.96		NR	
Foreign body sensation	0.5 / 0 / 0.5	0 / 0.5 / 0	0 / 0 / 1.9	0.6 / 0.6 / 0
	P = 0.17 / 0.38 / 0.46		NR	
Total symptom score, mean (SD), *P* value[d]				
Day 15 (N = 209 and 186)	0.25 (0.81)	0.40 (0.89)	NR	NR
	P = 0.085			
Day 42 (N = 208 and 186)	0.15 (0.51)	0.41 (1.03)	NR	NR
	P = 0.001			
Day 84 (N = 206 and 186)	0.18 (0.66)	0.46 (1.05)	NR	NR
	P = 0.001			
Disturbing or very disturbing ocular symptoms between instillations, % of patients, baseline / day 15 / day 42 / day 84, *P* value[a]				
Eye dryness sensation	3.8 / 3.3 / 1.4 / 1.0	0.5 / 2.2 / 3.2 / 3.2	NR	NR
	P = 0.85 / 0.92 / 0.59			
Foreign body sensation	1.9 / 1.0 / 1.4 / 0.5	2.1 / 0.5 / 1.6 / 1.0	NR	NR
	P = 0.72 / 0.89 / 0.50			
Irritation/burning/stinging	3.1 / 1.5 / 1.4 / 0.5	3.2 / 2.7 / 2.1 / 2.7	NR	NR
	P = 0.053 / 0.042 / 0.053			
Itching	2.3 / 1.4 / 1.0 / 1.0	1.6 / 2.2 / 1.6 / 3.2	NR	NR
	P = 0.76 / 0.34 / 0.20			
Photophobia	4.2 / 3.8 / 2.9 / 4.3	2.1 / 4.9 / 3.8 / 5.4	NR	NR
	P = 0.73 / 0.25 / 0.75			
Tearing	1.4 / 0.5 / 0 / 1.0	0.5 / 2.2 / 1.1 / 1.1	NR	NR
	P = 0.48 / 0.50 / 0.73			
Total symptom score, mean (SD), *P* value[e]				
Baseline	0.81 (1.92)	0.66 (1.49)	NR	NR
Day 15 (N = 209 and 186)	0.58 (1.53)	0.71 (1.54)	NR	NR
	P = 0.099			
Day 42 (N = 208 and 186)	0.47 (1.19)	0.65 (1.54)	NR	NR
	P = 0.057			
Day 84 (N = 206 and 186)	0.47 (1.37)	0.69 (1.73)	NR	NR
	P = 0.053			

LSM = least squares mean; NR = not reported; SD = standard deviation.

Note: All *P* values are provided for descriptive purposes only.

[a] Cochran–Mantel–Haenszel test stratified by country. Analysis was done on numbers of patients in each of the categories of severity.

[b] Screening visit was 42 days before baseline for L2345-PIII-12/08 and seven to 10 days before baseline for LT2345-001.

[c] Analysis of covariance on change from baseline adjusted for pooled site and baseline value.

[d] Analysis of variance adjusted for country.

[e] Analysis of covariance adjusted for country and baseline value.

Source: Clinical Study Reports.[6,8]

Harms

Adverse Events

In both studies, ocular AEs occurred in a greater proportion of patients in the Xalatan group than in the Monoprost group. Ocular AEs occurred in 9% and 12% of patients in the Monoprost and Xalatan groups, respectively, in the pivotal study and 14% and 23% of patients in the Monoprost and Xalatan groups, respectively, in the supportive study. Withdrawals due to AEs were rare (less than two patients per group, see Table 11). The most frequent ocular AEs were pain at the instillation site, conjunctival hyperemia, and punctate keratitis. The AEs conjunctival hyperemia, allergic conjunctivitis, blepharitis, drug intolerance, punctate keratitis, and pain at the instillation site were numerically more frequent in the patients taking Xalatan, although the proportions of patients with each AE were low (5% or less) in all cases.

Serious Adverse Events

There were no serious ocular AEs reported in either study. Systemic serious AEs were present in 2% or less of patients in each treatment group (Table 11).

Withdrawals Due to Adverse Events

In the pivotal study, three patients in the Monoprost group withdrew early due to adverse events (drug intolerance, eye pruritus, and major depression), as did one patient in the Xalatan group (allergic conjunctivitis and migraine in the same patient). In the supportive study, one patient in the Monoprost group withdrew early due to conjunctivitis in both eyes, and one patient in the Xalatan group withdrew early due to blepharitis and conjunctival hyperemia in both eyes.

Mortality

One patient in the Xalatan group in the supportive study died from metastatic melanoma. There were no other deaths in either study.

Notable Harms

Proportions of patients with notable harms identified in the systematic review protocol were low in both studies and similar between groups, as described above.

Table 11: Harms

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 213 Safety Set	**Xalatan N = 189 Safety Set**	**Monoprost N = 164[a] Safety Set**	**Xalatan N = 167[a] Safety Set**
Subjects with ≥ 1 ocular AE, n (%)	18 (9)	22 (12)	23 (14)	38 (23)
WDAE, n (% of safety set)	2 (0.9)	1 (0.5)	1 (0.6)	1 (0.6)
SAE, n (% of safety set)	0	0	0	0
Most common ocular AEs (> 1% in at least 1 group), n (%)				
Blepharitis[b]	1 (0.5)	0	2 (1)	5 (3)
Conjunctival cyst	NR	NR	0	2 (1)

	Study LT2345-PIII-12/08		Study LT2345-001	
Conjunctival hemorrhage	0	0	0	2 (1)
Conjunctival hyperemia[b]	1 (0.5)	3 (2)	3 (2)	4 (2)
Conjunctivitis allergic	1 (0.5)	3 (2)	0	2 (1)
Corneal staining	1 (0.5)	2 (1)	1 (0.6)[c]	0
Drug intolerance[b]	1 (0.5)	4 (2)	NR	NR
Dry eye[b]	1 (0.5)	2 (1)	1 (0.6)	1 (0.6)
Eye pain	0	2 (1)	0	1 (0.6)
Foreign body sensation in eyes[b]	1 (0.5)	2 (1)	1 (0.6)	0
Instillation site pain	NR	NR	3 (2)	8 (5)
Instillation site pruritus[b]	NR	NR	2 (1)	1 (0.6)
Instillation site abnormal sensation	NR	NR	1 (0.6)	2 (1)
Instillation site complication	NR	NR	0	2 (1)
Photophobia[b]	1 (0.5)	2 (1)	0	1 (0.6)
Punctate keratitis[b]	1 (0.5)	2 (1)	1 (0.6)	5 (3)
Vision blurred[b]	1 (0.5)	3 (2)	1 (0.6)	0
Vitreous detachment	1 (0.5)	0	1 (0.6)	2 (1)
Additional notable AEs				
Eye irritation	1 (0.5)	1 (0.5)	0	1 (0.6)
Eye pruritus	2 (0.9)	1 (0.5)	1 (0.6)	1 (0.6)
Lacrimation increased	0	1 (0.5)	1 (0.6)	0
Subjects with ≥ 1 systemic AE, n (%)	28 (13)	32 (17)	27 (16)	23 (14)
WDAE, n (% of safety set)	1 (0.5)	1 (0.5)[b]	0	2 (1)
SAE, n (% of safety set)	5 (2)	1 (0.5)	1 (0.6)	4 (2)
Most common systemic AEs (> 1% in at least 1 group), n (%)				
Back pain	0	1 (0.5)	2 (1)	1 (0.6)
Bronchitis	0	3 (2)	1 (0.6)	2 (1)
Bronchitis	0	3 (2)	1 (0.6)	2 (1)
Dizziness	0	2 (1)	NR	NR
Headache	2 (0.9)	4 (2)	1 (0.6)	0
Hypertension	0	2 (1)	1 (0.6)	0
Muscle spasms	1 (0.5)	0	0	2 (1)
Nasopharyngitis	2 (0.9)	1 (0.5)	1 (0.6)	2 (1)
Oropharyngeal pain	0	2 (1)	NR	NR
Sciatica	NR	NR	1 (0.6)	2 (1)
Sinusitis	1 (0.5)	0	2 (1)	0
Tooth infection	1 (0.5)	2 (1)	NR	NR
Urinary tract infection	0	3 (2)	3 (2)	0
Number of deaths, n (%)	0	0	0	1 (0.6)

AE = adverse event; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Patients with available data.

[b] Notable harm identified in the systematic review protocol.

[c] Listed as corneal disorder.

Source: Clinical Study Reports.[6,8]

Discussion

Summary of Available Evidence

The results from two phase III RCTs comparing Monoprost with Xalatan for outcomes related to efficacy, safety, and tolerability are presented in this systematic review. One RCT was a pivotal study and one was a supportive study, with clinical study reports for both RCTs provided by the manufacturer.[6,8] A publication was available for the pivotal study.[7] An open-label, phase IV study[9] comparing Monoprost and Xalatan was identified in the literature search and is summarized in Appendix 6. An additional search for indirect comparisons and network meta-analyses identified one publication comparing Monoprost with PGAs,[10] and this is summarized in Appendix 7.

Interpretation of Results

Efficacy

Results from the pivotal and supportive phase III RCTs indicated that mean IOP-lowering efficacy from baseline to days 15, 42, and 84 was similar between Monoprost and Xalatan. Noninferiority in efficacy of Monoprost to Xalatan was established in the pivotal study. In the supportive study, mean change in study eye IOP from baseline between Monoprost and Xalatan met the 1.5 mm Hg equivalence criterion but not the 1.0 mm Hg criterion that needed to be met by the majority of the measurements. Analysis of IOP change in the contralateral eye, which was the eye with the higher IOP at baseline, met both equivalence criteria, with five of nine measurements meeting the 1.0 mm Hg margin. Although efficacy was similar between the two treatments, IOP was consistently higher post-baseline in the Monoprost group in the phase III RCTs and the phase IV RCT. The mean differences were less than 1.0 mm Hg and were not considered clinically important by the clinical expert consulted for this review.

The Health Canada Pharmaceutical Safety and Efficacy Assessment accompanying the Notice of Deficiency for Monoprost[26] considered the measurement of IOP at only one time point during the day a major limitation in the pivotal study. The manufacturer subsequently provided the report for the supportive study, in which IOP was measured three times during the day, in response to the Notice of Deficiency.[25] The Health Canada review of the response to the Notice of Deficiency also contained results for the primary efficacy end point of the pivotal study using a modified PP set, which excluded all major protocol violations.[25] Noninferiority was accepted in this analysis.[25]

Direct comparisons between Monoprost and any of the other available PGAs were not available, although indirect comparisons were conducted by Cucherat et al.[7] The results indicated that IOP after three months of study treatment was similar between Monoprost and bimatoprost 0.03%, bimatoprost 0.01%, and BAK-free travoprost, although slightly higher in patients on Monoprost (mean differences of 0.19 mm Hg to 0.49 mm Hg). The mean difference in IOP lowering from baseline to three months between Monoprost and bimatoprost 0.03% was 0.94 mm Hg in favour of bimatoprost 0.03%. Indirect comparisons were not available from Monoprost versus sofZia- or polyquaternium-1–preserved travoprost for IOP outcomes. Risk of bias in IOP measurements is low, given their objective nature, and measurements in the phase III and IV RCTs were taken at consistent time points using an appropriate instrument in the RCTs. However, there may have been heterogeneity in the IOP outcomes of the indirect comparisons meta-analysis due to

differences in the instruments used for measuring IOP and uncertainty in whether the IOP results were adjusted for baseline IOP. Patients randomized in the pivotal study had been on latanoprost monotherapy for at least nine months and were therefore known to respond to the active ingredient in both study drugs.

Tolerability and Safety

Outcomes other than the primary efficacy outcomes in the phase III studies were not controlled for type I error and should be treated as exploratory in nature. The studies were not powered to assess outcomes other than the primary efficacy outcomes.

The presence and severity of the ocular symptoms of pruritus, burning/stinging, blurred vision, sticky eye sensation, eye dryness sensation, or foreign body sensation upon instillation were reported by patients in both phase III studies. The scale used to assess severity was not a validated instrument. Symptoms rated by patients as “disturbing” or “very disturbing” were present in less than 4% of patients in each treatment group at each time point. While the score distributions tended to be more severe in the Monoprost group for burning/stinging at all time points in the pivotal study, the absolute differences in percentage between groups were less than 3% for patients with disturbing burning/stinging. Similar symptoms between instillations were reported by patients in both phase III studies and were “disturbing” or “very disturbing” in less than 6% of patients in each treatment group at each time point. Score distributions were similar for all symptoms except for irritation/burning/stinging. Absolute differences in percentages of patients who rated irritation/burning/stinging as disturbing between groups were less than 3%. According to the clinical expert consulted for this review, someone with ocular symptoms between instillations may be more likely to experience ocular symptoms upon instillation, since the ocular surface would already be irritated.

In the phase IV study, percentages of patients on Xalatan with bothersome ocular symptoms were reduced from baseline to three months for all symptoms during instillation and for two symptoms between instillations (absolute reductions of up to 8%). This is despite the fact that these patients were already on BAK-preserved latanoprost monotherapy before the study. Patients in the Monoprost group had larger reductions in proportions of those with bothersome symptoms (absolute reductions of 6% to 23%), especially dryness, irritation/tingling/burning, and foreign body sensation. The proportions of patients with ocular symptoms at baseline were higher in the phase IV study than in the phase III studies.

According to the clinical expert consulted for this review, ocular symptoms of “disturbing” or “very disturbing” severity may be present in a small percentage of the general population and are not specific to OSD. The clinical expert also noted that symptoms between instillation would be more important to patients than symptoms upon instillation, due to longer duration. The lack of patient blinding to treatment allocation means that symptoms rated by patients may have been susceptible to bias. If patients on Monoprost expected to experience less ocular symptoms, the potential benefits observed with Monoprost may have been overestimated.

The six-point McMonnies photographic scale was used to assess conjunctival hyperemia in the phase III studies. In the pivotal study, severe hyperemia (score of 5 or 6) was not observed in any of the patients after baseline. Although score distributions differed between groups at days 42 and 84, the percentages of patients with moderate hyperemia (score of 3 or 4) were only 4.9% and 5.3%, respectively, in the Monoprost group and 8.6% and 7.6%,

respectively, in the Xalatan group. In the supportive study, the mean hyperemia score did not differ between the treatment groups. According to the clinical expert consulted for this review, patients with the same hyperemia severity may be bothered by it to different degrees. Also, there was no information found on the responsiveness or MCID for the scale. The clinical expert did not consider small decreases in percentages of patients with scores on the McMonnies scale of 3 or 4 to be clinically meaningful. Only 2% or less of patients in each group in both studies reported conjunctival hyperemia as an adverse event, suggesting that most patients with some degree of conjunctival hyperemia were not bothered by it.

Severity of conjunctival hyperemia, as assessed on the five-point Efron scale in the phase IV study, was reduced to a greater extent in the Monoprost group, although there were no patients in the highest category of severity, and the mean score reduction of 0.5 in the Monoprost group was of unclear clinical importance. Unlike in the phase III studies, investigators were not blinded to treatment allocation, and bias in hyperemia assessment was possible.

The indirect comparisons showed lower proportions of patients with hyperemia or ocular redness with Monoprost compared with sofZia-preserved travoprost, bimatoprost 0.03%, and bimatoprost 0.01% (odds ratios from 0.18 to 0.52). However, only one study that compared Monoprost with another drug was included (the pivotal study from this review). Pooling of hyperemia estimates was likely inappropriate, as the outcome was not well defined; for example, incidence of hyperemia at least two studies was based on patient reporting of adverse events.

Investigators globally assessed local tolerance in the pivotal study, although this outcome measure is not a validated instrument. Distributions of ratings were more favourable for the Monoprost group, although most of the differences were in the “very satisfactory” and “satisfactory” categories. Investigator-assessed tolerance was at least satisfactory for almost all patients (98% or more in both treatment groups). Although slightly more patients in the Monoprost group than in the Xalatan group felt that treatment was convenient, almost all patients (96% and above) felt that treatment was convenient regardless of study drug.

Results from a questionnaire in the phase IV study showed greater proportions of very satisfied patients and patients reporting improvement in impact of treatment on daily, work, and leisure activities in the Monoprost group than in the Xalatan group. However, a validated instrument was not used to assess patient satisfaction or quality of life.

The proposed benefits of Monoprost over BAK-preserved latanoprost, given similar IOP-lowering efficacy between the two, are improved safety and tolerability. Improved safety and tolerability may lead to improved quality of life for patients as well as improved adherence to the drug. In the phase III studies and phase IV study, tolerability was assessed by patient reporting of symptoms of ocular discomfort and investigator-determined conjunctival hyperemia severity. Health- and vision-related quality of life were not assessed using validated instruments in any of the studies. Due to the limitations in the outcomes reported and the small differences between treatment groups that were of unclear clinical importance, benefits of Monoprost over BAK-preserved latanoprost in terms of safety and tolerability were not well established.

Improved adherence may result in improved effectiveness of IOP lowering outside of clinical trials, although evidence for this association was not found in a supplemental literature search conducted for this review. Based on patient recall, a potentially unreliable

method of measuring compliance, the treatment protocol in the pivotal study was followed by a smaller proportion of patients in the Monoprost group than in the Xalatan group. Six patients in the pivotal study followed less than 70% of expected treatment administrations between visits, and all six patients were in the Monoprost group (i.e., 3% of the group). Compliance assessed by patient recall in the supportive study was similar between the groups and compliance data based on drug accounting was not informative because it was easier to count returned medication in the single-dose format. Compliance was not reported in the phase IV study.

Harms

There were no safety concerns raised in the phase III studies or the phase IV study, and withdrawals due to AEs were very limited. Ocular AEs occurred in 9% and 12% of patients in the Monoprost and Xalatan groups, respectively, in the pivotal study; 14% and 23% of patients in the Monoprost and Xalatan groups, respectively, in the supportive study; and 2% and 4% of patients in the Monoprost and Xalatan groups, respectively, in the phase IV study. The most common types of AEs were pain at the instillation site, conjunctival hyperemia, and punctate keratitis. Some AEs were more common in the Xalatan groups, although the proportions of patients with each AE were low (5% or less) in all cases. The clinical expert consulted for this review considered the AEs reported to be typical of this patient population and drug class. Patient knowledge of treatment allocation meant that bias in AE reporting could not be ruled out.

Potential Place in Therapy[2]

The current (2018) standard of care for the treatment of glaucoma is to reduce IOP, which is most often done with medications. There are several different classes of medications used to lower IOP, with the most common being PGAs. Most of the PGAs available in Canada are preserved with BAK, with the exception of Travatan Z, sofZia-preserved travoprost 0.004%, and Izba, polyquaternium-1–preserved travoprost 0.003%.

OSD includes a variety of conditions that affect the surface of the eye, notably the cornea and conjunctiva. OSD is common, affecting 15% of patients over 65.[12] However, in patients receiving glaucoma medical therapy, a prevalence of up to 60% has been reported.[13] OSD affects vision-related quality of life and may negatively affect compliance with glaucoma medical therapy. Inflammatory changes with OSD may negatively affect subsequent surgical outcomes. There is a lack of widely accepted criteria for diagnosing OSD, and correlation between clinical tests and OSD symptoms has been poor.[13]

The causes of OSD are multifactorial and include dry eye, blepharitis, and rosacea. However, OSD can also be caused or exacerbated by eye drops. The toxic or allergic effects from eye drops could be due to any of the constituents, including the active ingredient, the excipients, and/or the preservative. Since BAK is known to be cytotoxic, and long-term use of BAK can result in changes to the surface of the eye and exacerbate symptoms of OSD, the availability of a BAK-free PGA such as Monoprost could fill an unmet need.

However, the safety profiles of Travatan Z and Izba (preserved with alternatives to BAK) are similar to the safety profile of BAK-preserved travoprost in terms of OSD symptoms reported as adverse events,[14,15] suggesting that BAK may have only a limited role in OSD.

[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.

The currently marketed BAK-free PGAs do not appear to fulfill the unmet need for the reduction of OSD symptoms.

With its higher price, Monoprost would need to demonstrate a significant reduction in OSD symptoms over other PGAs to be considered as a first-line treatment for the reduction of IOP in patients with no contraindications to a PGA. Given the lack of such evidence, it could be considered as a second-line PGA for patients unable to tolerate a PGA due to severe OSD.

Conclusions

Results from the two included phase III studies showed similar IOP-lowering efficacy of Monoprost when compared with Xalatan (i.e., BAK-preserved latanoprost) over a period of three months. Similar results were shown in an open-label phase IV study. An indirect treatment comparison meta-analysis indicated similar IOP-lowering efficacy of Monoprost compared with bimatoprost (both the 0.03% and 0.01% formulations), although the study had limitations. Direct or indirect comparisons of IOP outcomes of Monoprost versus other comparators currently available in Canada were not available.

Assessment of conjunctival hyperemia and symptoms of ocular discomfort in the phase III studies and phase IV study suggested favourable tolerability of Monoprost compared with Xalatan, but limitations in the outcomes reported and small differences between treatment groups meant that the benefits of Monoprost were uncertain and of unclear clinical importance. The indirect treatment comparisons also suggested lower incidence of conjunctival hyperemia with Monoprost compared with sofZia-preserved travoprost and BAK-preserved bimatoprost, but these results were associated with limitations. While some AEs were more common in the Xalatan group than in the Monoprost group, the proportions of patients with each AE were low (5% or less). Visual acuity and the incidence of abnormalities in the anterior segment of the eye did not differ between the Monoprost and Xalatan groups. There was no evidence of differences in treatment compliance between the Monoprost and Xalatan groups.

Appendix 1: Patient Input Summary

No input was provided by patient groups for this review.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily; Ovid MEDLINE(R) 1946 to Present; Embase 1974 to present.
Date of Search:	November 21, 2017
Alerts:	Weekly search updates until March 21, 2018
Study Types:	Randomized controlled trial filter
Limits:	No date or language limits were used. Conference abstracts were excluded.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as 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#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1.	(monoprost* or latanoprost* or xalatan* or phxa41 or phxa 41 or xa41 or xa 41 or 6z5b6hvf60 or akistan* or glaukadoc* or latacris* or latalux* or lataniston* or latano pos or latano vision* or latanomed* or latanopos* or latanostad* or latanovision* or latizolil* or latop* or louten* or oftastad* or pharmaprost* or pharmecol* or phxa34 or phxa 34 or polprost* or proxal* or rozaprost* or tonlit* or xaloptic* or xalost* or zakoprost*).ti,ab,hw,nm,kf,ot,rn.
2.	130209-82-4.rn,nm.
3.	1 or 2
4.	(monoprost* or latanoprost* or xalatan* or phxa41 or phxa 41 or xa41 or xa 41 or 6z5b6hvf60 or akistan* or glaukadoc* or latacris* or latalux* or lataniston* or latano pos or latano vision* or latanomed* or latanopos* or latanostad* or latanovision* or latizolil* or latop* or louten* or oftastad* or pharmaprost* or pharmecol* or phxa34 or phxa 34 or polprost* or proxal* or rozaprost* or tonlit* or xaloptic* or xalost* or zakoprost*).ti,ab,kw.
5.	*latanoprost/
6.	4 or 5
7.	3 use ppez
8.	6 use oemezd

MULTI-DATABASE STRATEGY
9. 7 or 8
10. Randomized Controlled Trial.pt.
11. Pragmatic Clinical Trial.pt.
12. exp Randomized Controlled Trials as Topic/
13. "Randomized Controlled Trial (topic)"/
14. Randomized Controlled Trial/
15. Randomization/
16. Random Allocation/
17. Double-Blind Method/
18. Double-Blind Procedure/
19. Double-Blind Studies/
20. Single-Blind Method/
21. Single Blind Procedure/
22. Single-Blind Studies/
23. Placebos/
24. Placebo/
25. (random* or sham or placebo*).ti,ab,hw,kf,kw.
26. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
27. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
28. or/10-27
29. 9 and 28
30. conference abstract.pt.
31. 29 not 30
32. remove duplicates from 31

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 2017
Keywords:	Drug name
Limits:	Randomized controlled trial filter

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
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Aptel F, Choudhry R, Stalmans I. Preservative-free versus preserved latanoprost eye drops in patients with open-angle glaucoma or ocular hypertension. Curr Med Res Opin. 2016 Aug;32(8):1457-63.	Phase II study
Chhabra H, Gupta A, Singh G. A comparative study of benzalkonium chloride-free latanoprost versus benzalkonium chloride-preserved latanoprost on ocular surface health in patients of primary open-angle glaucoma. International Journal of Basic & Clinical Pharmacology [Internet]. 2017 [cited 2017 Dec 15];6(5).	Irrelevant intervention
Clinical Study Report: Report Number L2345-1007(IN). pharmacokinetics, efficacy and safety assessment of unpreserved latanoprost 0.005% ophthalmic preparation (T2345) compared with preserved latanoprost 0.005% eye drops (Xalatan®) in newly diagnosed patients with open-angle glaucoma or ocular hypertension. [**CONFIDENTIAL** internal manufacturer's report]. Clermont-Ferrand [France]: Laboratoires Théa; 2009.	Phase II study
Cucherat M, Stalmans I, Rouland JF. Relative efficacy and safety of preservative-free latanoprost (T2345) for the treatment of open-angle glaucoma and ocular hypertension: an adjusted Indirect comparison meta-analysis of randomized clinical trials. J Glaucoma. 2014 Jan;23(1):e69-e75.	Meta-analysis; summarized in Appendix 7.
Denis P, Monoprost French Study Group. Unpreserved latanoprost in the treatment of open-angle glaucoma and ocular hypertension. A multicenter, randomized, controlled study. J Fr Ophtalmol. 2016 Sep;39(7):622-30.	Phase IV study; summarized in Appendix 6.
Stalmans I, Oddone F, Cordeiro MF, Hommer A, Montesano G, Ribeiro L, et al. Comparison of preservative-free latanoprost and preservative-free bimatoprost in a multicenter, randomized, investigator-masked crossover clinical trial, the SPORT trial. Graefes Arch Clin Exp Ophthalmol. 2016 Jun;254(6):1151-8.	Phase IV study, irrelevant comparator
Walimbe T, Chelerkar V, Bhagat P, Joshi A, Raut A. Effect of benzalkonium chloride-free latanoprost ophthalmic solution on ocular surface in patients with glaucoma. Clin Ophthalmol. 2016;10:821-7.	Irrelevant intervention

Appendix 4: Detailed Outcome Data

Table 12: Additional Outcomes Related to Intraocular Pressure

	Study LT2345-001	
	Monoprost N = 161 PP Set	**Xalatan N = 164 PP Set**
Mean study eye IOP, mm Hg, mean (95% CI)		
Screening		
8:00 a.m.	15.5 (2.3)	15.6 (2.2)
10:00 a.m.	15.5 (2.2)	15.5 (2.4)
4:00 p.m.	15.4 (2.5)	15.5 (2.3)
Diurnal[a]	15.5 (2.0)	15.5 (1.9)
Baseline		
8:00 a.m.	19.6 (3.3)	19.6 (3.3)
10:00 a.m.	18.6 (3.5)	19.1 (3.6)
4:00 p.m.	18.4 (3.0)	18.9 (3.5)
Diurnal[a]	18.8 (2.9)	19.2 (3.1)
Day 15		
8:00 a.m.	16.5 (3.1)	15.7 (3.1)
10:00 a.m.	15.9 (2.9)	15.5 (2.8)
4:00 p.m.	16.1 (2.7)	15.7 (2.9)
Diurnal[a]	16.2 (2.6)	15.7 (2.6)
Day 42		
8:00 a.m.	16.5 (3.1)	16.0 (3.1)
10:00 a.m.	15.9 (2.9)	15.6 (2.8)
4:00 p.m.	16.1 (3.0)	15.8 (2.8)
Diurnal[a]	16.2 (2.6)	15.8 (2.6)
Day 84		
8:00 a.m.	16.6 (2.9)	15.8 (2.7)
10:00 a.m.	15.9 (2.9)	15.5 (2.9)
4:00 p.m.	16.2 (2.8)	15.9 (2.9)
Diurnal[a]	16.3 (2.6)	15.7 (2.5)
Patients with study eye IOP < 18 mm Hg, n (%)		
Screening		
8:00 a.m.	133 (83)	131 (80)
10:00 a.m.	133 (83)	132 (81)
4:00 p.m.	133 (83)	133 (81)
Diurnal[a]	144 (89)	149 (91)
Baseline		
8:00 a.m.	48 (30)	44 (27)
10:00 a.m.	65 (40)	57 (35)

	Study LT2345-001	
4:00 p.m.	59 (37)	57 (35)
Diurnal[a]	62 (39)	53 (33)
Day 15, diurnal[a]	118 (73)	126 (77)
Day 42, diurnal[a]	121 (75)	127 (78)
Day 84, diurnal[a]	117 (73)	129 (79)

CI = confidence interval; IOP = intraocular pressure; PP = per-protocol.

Note: If both eyes were eligible, the study eye was the eye with lower baseline IOP. If both eyes had the same baseline IOP, the right eye was the study eye.

[a]Diurnal IOP was the average of the IOP measurements at the three times of day.

Source: Clinical Study Report.[6]

Table 13: Additional Efficacy Outcomes

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 213 Safety Set	**Xalatan N = 189 Safety Set**	**Monoprost N = 165 Safety Set**	**Xalatan N = 170 Safety Set**
Visual field in study eye, mean (SD)				
Screening[a]	NR	NR	–1.2 (2.5)	–1.6 (2.5)
Day 84	NR	NR	–1.4 (2.6)	–1.7 (2.8)
Patients with abnormal visual field with glaucomatous defect in study eye, n (%)				
Screening[a]	NR	NR	20 (12)	32 (19)
Day 84	NR	NR	21 (13)	30 (18)
Cup-to-disc ratio in the study eye, mean (SD)				
Screening[a]	0.45 (0.18)	0.45 (0.17)	0.50 (0.17)	0.50 (0.17)
Day 84 (N = 70 and N = 53 for LT2345-PIII-12/08)	0.42 (0.18)	0.48 (0.15)	0.50 (0.17)	0.50 (0.17)

NR = not reported; SD = standard deviation.

[a] Screening visit was 42 days before baseline for L2345-PIII-12/08, seven to 10 days before baseline for LT2345-001.

Source: Clinical Study Reports.[6,8]

Table 14: Additional Tolerability Outcomes

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 213 Safety Set	**Xalatan N = 189 Safety Set**	**Monoprost N = 165 Safety Set**	**Xalatan N = 170 Safety Set**
Investigator's global assessment of local tolerance, % of patients, Very satisfactory / Satisfactory / Not very satisfactory / Unsatisfactory, *P* value[a]				
Day 15	65 / 34 / 0.5 / 0.5	60 / 38 / 2 / 0.5	67 / 31 / 2 / 0	66 / 33 / 1 / 0
	P = 0.17		NR	
Day 42	74 / 25 / 0.5 / 0.5	65 / 33 / 2 / 0	69 / 31 / 1 / 0	63 / 36 / 1 / 0
	P = 0.013		NR	
Day 84	71 / 27 / 1 / 0	63 / 35 / 2 / 0	73 / 25 / 1 / 1	76 / 24 / 0 / 0
	P = 0.047		NR	
Patients who felt treatment was convenient, n (%), *P* value[a]				
Day 15	206 (99)	181 (97)	NR	NR
	P = 0.38			

	Study LT2345-PIII-12/08		Study LT2345-001	
Day 42	205 (99)	177 (96)	NR	NR
	P = 0.056			
Day 84	206 (99.5)	179 (96)	NR	NR
	P = 0.016			

NR = not reported.

[a]Cochran–Mantel–Haenszel test stratified by country. Analysis was done on numbers in each category.

Source: Clinical Study Reports.[6,8]

Table 15: Additional Safety Outcomes

	Study LT2345-PIII-12/08		Study LT2345-001	
	Monoprost N = 213 Safety Set	**Xalatan N = 189 Safety Set**	**Monoprost N = 165 Safety Set**	**Xalatan N = 170 Safety Set**
Corrected Snellen visual acuity[a], mean (SD)				
Screening[b]	8.9 (1.7)	8.9 (1.8)	0.092 (0.104)	0.085 (0.108)
Baseline	9.0 (1.7)	8.8 (1.8)	0.087 (0.099)	0.079 (0.099)
Day 15	NR	NR	0.081 (0.098)	0.077 (0.095)
Day 42	NR	NR	0.080 (0.096)	0.078 (0.095)
Day 84	9.0 (1.7)	8.9 (1.7)	0.082 (0.095)	0.069 (0.101)
Clinically significant abnormalities on slit-lamp examination in the study eye, % of patients, Screening[b] / baseline / day 15 / day 42 / day 84				
Lid	NR	NR	1.8 / 1.8 / 1.8 / 1.8 / 2.5	0.6 / 0.6 / 0 / 1.2 / 0
Cornea	NR	NR	0.6 / 0.6 / 0 / 0.6 / 0.6	0 / 0 / 0 / 0.6 / 1.2
Conjunctiva	NR	NR	1.2 / 0.6 / 1.8 / 1.8 / 1.2	0 / 0 / 0 / 0 / 0
Iris	NR	NR	0 / 0 / 0.6 / 0 / 0	0.6 / 0.6 / 0.6 / 1.2 / 0.6
Lens	NR	NR	1.8 / 1.8 / 1.8 / 2.5 / 1.9	4.1 / 2.4 / 3.6 / 3.0 / 3.6
Ocular signs on slit-lamp examination in the study eye, *P* values[c] for day 15 / day 42 / day 84				
Palpebral abnormality[d]	*P* values: 0.84 / 0.20 / 0.46		NR	
Folliculo-papillary conjunctivitis[d]	*P* values: 0.43 / 0.39 / 0.91		NR	
Anterior chamber flare[d]	*P* values: NR / 0.17 / 0.72		NR	
Corneal staining punctuations[e]	*P* values: 0.55 / 0.23 / 0.12		NR	

NR = not reported; SD = standard deviation.

Note: All *P* values are provided for descriptive purposes only.

[a] Represented as /10 for L2345-PIII-12/08; converted to logarithm of (1 / visual acuity in decimals) for LT2345-001.

[b] Screening visit was 42 days before baseline for L2345-PIII-12/08, seven to 10 days before baseline for LT2345-001.

[c] Cochran–Mantel–Haenszel test based on numbers of patients in each category of severity and stratified by country.

[d] Categories: absent, mild, moderate, and severe.

[e] Categories: absent; some; < 10% / diffused; ≤ 50% / diffused; > 50%.

Source: Clinical Study Reports.[6,8]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Goldmann applanation tonometry (GAT)
- Intraocular pressure (IOP)
- McMonnies photographic scale

Findings

Goldmann applanation tonometry

GAT is identified as the gold standard in measuring IOP and is recommended as such by the Canadian Ophthalmological Society glaucoma guidelines and the UK National Institute for Health and Care Excellence (NICE) glaucoma guidelines.[3,36-38] In study LT2345-PIII-12/08, the investigators took two consecutive IOP measurements in each eye. If the results differed by 2 mm Hg or less, a third measurement was conducted. Subsequently, the average of the two (or three) readings was taken as the patient's IOP.[30] In study LT2345-001, the provided clinical study report indicates no more than one measurement at each visit.[34]

The reliability of IOP measurement using GAT has been established.[36,37] In a study conducted by Dielemans et al.,[37] 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 between the first IOP reading and the 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 conclude 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.[37]

A second study conducted by Sudesh et al. examined accuracy and variability in IOP measurement using GAT.[36] 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 by 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 [SE] 0.44). The first set of four readings had a higher mean IOP than the second set of readings (difference 0.71 mm Hg, SE 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 or more for 26% of observers and 3 mm Hg or more for 19% of observers.[36]

These two studies suggest that GAT produces reliable IOP readings. 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. Study LT2345-PIII-12/08 attempted to address variability by repeating IOP measurements (up to three times) and reporting an average reading. Study LT2345-001 did not report whether similar measures were taken to address IOP variability.

Intraocular Pressure

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 Ophthalmological Society recommends assigning an IOP upper threshold as a goal of therapy based on the severity of glaucoma, as follows:[3]

- Suspect in 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.

The suggested upper limit of target IOP should be modified based on patient's age, life expectancy, quality of life, and risk factors for progression.[3]

Correlation of Intraocular Pressure Lowering With Clinical Outcomes

A 2013 systematic review by the US Preventive Services Task Force assessed the result of medical treatment on visual field loss and optic nerve damage in open-angle glaucoma.[39] 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 risk of optic nerve damage and visual field loss. However, insufficient evidence was present on the effect of glaucoma treatment on patient-reported outcomes (quality of life, activity limitation, patient-reported visual loss).

The effect of treating ocular hypertension and open-angle glaucoma compared with no treatment was evaluated in a 2005 systematic review and meta-analysis.[40] The study included a meta-analysis of five RCTs of patients with ocular hypertension, and the results indicated that reducing IOP 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-analysis of two of the included RCTs indicated that treatment of 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.

Clinical Correlation of Lack of Adherence and Intraocular Pressure Changes

The pharmacoeconomic model in the Monoprost CADTH Common Drug Review submission[24] used the assumption that lack of treatment adherence causes an increase of 2 mm Hg in IOP measurements.[41] This assumption was based on a 2010 prospective observational study that surveyed the characteristics of 113 patients with open-angle glaucoma or ocular hypertension using a specific electronic device measuring the number of drops instilled each day after eight weeks of use. The authors of the study reported that, at the end of the eight-week period, patients with low compliance had a mean IOP of 17.7 mm Hg (SD 5.3), while patients with mid- to high compliance had a mean IOP of 15.7 mm Hg (SD 3.3).[42] The authors of the study cautioned against generalizing the results of the survey to the general glaucoma population, as the sample was not recruited randomly, patients knew their compliance was being evaluated, and the duration of assessment was short.[42]

A supplemental literature search was conducted for this review for additional studies to support the assumption that lack of adherence causes a 2 mm Hg increase in IOP measurement. No additional relevant studies were found. Even the authors of the study cited by the manufacturer's submission indicated that another study found the mean IOP to be 22.9 mm Hg in noncompliant patients versus 18.5 mm Hg in compliant patients.[43] This study assessed compliance and glaucoma awareness in a 100 Greek patients taking eye drops for glaucoma; the study determined that 56% of patients had satisfactory treatment compliance, with a mean IOP of 18.6 mm Hg (SD 3.5), in contrast to a mean IOP of 22.9 mm Hg (SD 3.7) in noncompliant patients.[43] Hence, there is a high level of uncertainty and insufficient evidence to assume that lack of compliance translates into a difference in IOP of 2 mm Hg.

McMonnies Photographic Scale

The McMonnies photographic scale is a six-level scale (in which 0 represents minimal hyperemia and 5, maximum hyperemia) originally developed for the assessment of bulbar hyperemia in contact lens wearers.[28] The scale provides a photographic reference for each grade, and the examiner determines which one most closely resembles the patient's degree of hyperemia. To assess for inter-observer reliability, two investigators independently assessed the right eye of 18 participants with a resulting Spearman rank correlation coefficient (rho) of 0.62. To assess for intra-observer reliability, each of the two investigators assessed the right eye of 19 participants twice, with a resulting rho value of 0.83.[28] A study in which digitally assessed physical qualities of the reference images of the McMonnies photographic scale found that the scale was correlated (Pearson correlation coefficients 0.94 to 0.98) with measures of vascular branching complexity, blood vessel coverage, and photometric chromaticity.[29] No MCID was identified to support the clinical relevance of changes in the scale.

In patients who do not wear contact lenses over a wide range of ages (one year to 82 years), the mean score and SD on the original McMonnies scale (0 to 5) were 0.86 and 0.70.[28] On average, scores in men were about 0.5 scale units higher than those in women, and scores may increase with age.[28]

Table 16: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
Goldmann applanation tonometry	A clinical technique to measure IOP through determining the force needed to flatten a certain area of the cornea.	Yes	N/A	Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee 2009,[3] Sudesh et al. 1993,[37] Dielemans et al. 1994[37]
IOP	Measured through tonometry procedures, this outcome guides diagnosis, treatment, and prognosis of increased intraocular pressure and open-angle glaucoma. Potential prognostic quantification is based on changes in the IOP. Manufacturer used a change of 2 mm Hg as the difference in IOP measurements between treatment compliant and noncompliant patients.	N/A	Unknown	Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee 2009[3]
McMonnies photographic scale	Six-level scale with reference images of bulbar hyperemia	Yes	Unknown	McMonnies and Chapman-Davies 1987,[28] Schulze et al. 2008[29]

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

Conclusion

Using GAT to measure IOP is considered the gold standard by several professional bodies, including the Canadian Ophthalmological Society. Evidence suggests that GAT provides reliable measurements. However, there is a potential variation of 1 mm Hg to 2 mm Hg with measurement, which may depend on operator and time of measurement. A systematic review and meta-analysis of five RCTs of patients with ocular hypertension and open-angle glaucoma found that reducing IOP decreased the rate of progression to glaucoma compared with no treatment. The McMonnies photographic scale provides adequate intra-rater reliability, moderate level of inter-rater reliability, and strong correlations with the physical and photometric properties of the reference images.

Appendix 6: Summary of Other Studies

Introduction

One study retrieved from the literature search for randomized controlled trials (RCTs) compared Monoprost with latanoprost preserved with benzalkonium chloride (BAK), but it was a phase IV trial.[9] The results from this study by Denis et al.[9] are summarized in this appendix to provide additional information on comparative efficacy, safety, and tolerability of Monoprost. Details on the design of the study are provided in Table 17.

A supplemental literature search for Monoprost studies of non-RCT design to capture additional safety data did not find any relevant studies.

Table 17: Study Details

		Denis et al.[9]
Designs & Populations	**Study Design**	Phase IV, open-label, parallel-groups RCT
	Locations	58 centres in France
	Randomized (N)	183 (2:1 ratio of intervention: comparator)
	Inclusion Criteria	- Age 18 to 90 years - OAG or chronic ocular hypertension - Both eyes treated for at least six months with BAK-preserved latanoprost 0.005% monotherapy - No particular intolerance - Stable intraocular pressure (IOP) of ≤ 18 mm Hg - The study eye was the eye with the higher IOP or the right eye in the absence of a difference in IOP
	Exclusion Criteria	- Aphakia - History of refractive surgery - Ocular trauma, infection, or inflammation in the three months before inclusion - Previous uncontrolled asthma, any acute or chronic pathology determined by the investigator to be incompatible with the study
Drugs	**Intervention**	One drop q.d. of Monoprost (preservative-free latanoprost 50 µg/mL) in diseased eye(s) once daily at 9:00 p.m.
	Comparator	One drop q.d. of Xalatan (BAK-preserved latanoprost 50 µg/mL) in diseased eye(s) once daily at 9:00 p.m.
Duration	**Phase**	
	Run-in	N/A
	Treatment	3 months
	Follow-up	N/A
Outcomes	**Primary End Point**	Change from baseline to day 84 in IOP of the study eye measured with a Goldmann applanation tonometer (noninferiority to comparator)
	Other End Points	Efficacy: - Change from baseline to day 84 in IOP in contralateral eye - Patient-reported satisfaction and quality of life using a questionnaire Safety and tolerability: - Ocular signs on slit-lamp examination - Severity of conjunctival hyperemia - Patient-reported severity of ocular symptoms during and between instillations of study drug - Adverse events

BAK = benzalkonium chloride; IOP = intraocular pressure; N/A = not applicable; OAG = open-angle glaucoma; q.d. = once daily; RCT = randomized controlled trial.

Source: Denis et al.[9]

Methods

Study Design

Patients were randomized to Monoprost or Xalatan monotherapy in a 2:1 ratio. Details on randomization and allocation were not provided. Patients and investigators were not blinded to treatment allocation in this open-label study. Patients had to have been on BAK-preserved latanoprost monotherapy for both eyes for at least six months with controlled intraocular pressure (IOP) (≤ 18 mm Hg), and there was no medication washout period before the start of the study. Patients were assessed at baseline and three months later.

Interventions

One drop of study drug was administered in the diseased eye(s) once daily at 9:00 p.m. During the study, the following were not permitted: any other antiglaucoma or ocular treatments (with the exception of preservative-free artificial tears used in the short term), antihypertensive drugs, ocular topical steroids, topical or systemic nonsteroidal anti-inflammatory drugs, systemic immunosuppressants, and contact lens use.

Outcomes

IOP was measured three times at each visit at the same time of day with a calibrated and validated Goldmann applanation tonometer. One drop of fluorescein 0.05% and oxybuprocaine 0.4% solution was administered in each eye before IOP measurement. Noninferiority of Monoprost to Xalatan was tested using a noninferiority margin of 1.5 mm Hg for the difference between groups in change in IOP from baseline to day 84.

Slit-lamp ocular signs were scored from 0 to 3 according to severity (0 = none, 1 = light, 2 = moderate, 3 = severe): change in iris pigmentation, hypertrichosis (abnormal eyelash appearance), abnormal eyelid coloration, eyelid abnormalities, follicular papillary conjunctivitis, anterior chamber inflammation, and abnormal corneal staining.

Severity of conjunctival hyperemia was measured using the Efron photographic scale from 0 to 4.

Severity of ocular symptoms was scored on a scale of 0 to 3 (0 = none, 1 = present but not disturbing, 2 = disturbing, 3 = very disturbing) by the patient: dryness, irritation/tingling/burning, itching, tearing, foreign body sensation, and photophobia, both during and between instillations. A summary score was calculated by summing the score for each symptom in the eye with the higher degree of symptom severity.

A questionnaire at the end of the study on satisfaction and quality of life assessed treatment efficacy and impact of treatment on vision and on work, daily activities, and leisure activities.

Statistical Analysis

The sample size was based on a mean difference of 1.5 mm Hg or less and a standard deviation of 3 mm Hg for study eye IOP between the two treatment groups. A sample size of 252 patients (168 in the Monoprost group and 85 patients in the Xalatan group) corresponded to a power of 80% using a confidence interval (CI) of 95%.

Noninferiority was tested in the per-protocol (PP) set, which included all patients without missing data or major protocol deviations. The mean difference in IOP and its associated

95% CI was estimated using an analysis of covariance (ANCOVA) model adjusted for centre.

Continuous or quantitative outcomes were compared between treatment groups using the Wilcoxon test, and categorical outcomes were compared between groups using Fisher's exact test. A significance level of 5% was used for these tests, and only patients with complete data from both visits who received the study treatment were analyzed. No imputation was used for missing data, and there was no adjustment for multiple comparisons.

Results

Baseline Characteristics

Patients were recruited across 58 centres in France and ranged widely in age, with most patients being 60 to 80 years old. Both groups had been diagnosed for about the same length of time before the study (7.7 and 8.3 years in the Monoprost and Xalatan groups, respectively) and the average duration of treatment with preserved latanoprost was 5.3 years overall (standard deviation [SD] 3.5 years). While baseline IOP was the same in both groups, a greater proportion of patients in the Xalatan group had changed their antiglaucoma treatment at least once in the past five years (43% of patients in the Xalatan group versus 32% of patients in the Monoprost group). Half of these patients had switched treatment due to local intolerance. Overall, 23% of patients had a history of dry eye.

Efficacy

The 95% CI for the change in IOP from baseline to day 84 met the 1.5 mm Hg noninferiority margin for both the study eye and the contralateral eye. In the PP set, mean baseline IOP in the worse eye was 16.0 mm Hg (SD 2.5 mm Hg) in the Monoprost group (N = 114) and 15.9 mm Hg (SD 2.2 mm Hg) in the Xalatan group (N = 47). IOP in the worse eye at day 84 was 15.6 mm Hg (SD 2.8 mm Hg) in the Monoprost group and 14.9 mm Hg (SD 2.3 mm Hg) in the Xalatan group, leading to a change in IOP of –0.34 mm Hg (SD 2.14 mm Hg) in the Monoprost group and –0.94 mm Hg (SD 1.99 mm Hg) in the Xalatan group. The difference in IOP change in the Monoprost group versus the Xalatan group was 0.50 mm Hg (95% CI, –0.20 mm Hg to 1.21 mm Hg).

Safety and Tolerability

The proportion of patients with 2 or 3 on the Efron scale for conjunctival hyperemia was reduced in the Monoprost group compared with the Xalatan group (change from baseline to day 84 of –33% versus –6%). The mean score for conjunctival hyperemia in the study eye was also significantly reduced in the Monoprost group versus the Xalatan group (P = 0.0004).

The mean ocular symptoms score based on patient-reported symptoms decreased over the course of the study for both drugs, but the decrease was significantly greater in the Monoprost group with regard to both symptoms during instillation (mean –2.0, SD 2.7 for Monoprost versus mean –0.9, SD 2.2 for Xalatan; P = 0.0035) and between instillations (mean –1.9, SD 2.8 for Monoprost versus mean –0.3, SD 1.3 for Xalatan; P = 0.00030). The percentage of patients with disturbing or very disturbing ocular symptoms showed a greater decrease in the Monoprost group compared with the Xalatan group for all symptoms, most notably dryness and irritation/burning/tingling.

There were no significant changes in ocular signs on slit-lamp examination from baseline to day 84, except for small reductions in score for hypertrichosis and follicular papillary conjunctivitis in the Monoprost group compared with the Xalatan group (hypertrichosis: mean –0.3, SD 0.7 versus mean 0.0, SD 0.5; *P* = 0.0011; follicular papillary conjunctivitis: mean –0.2, SD 0.5 versus mean –0.0, SD 0.5; *P* = 0.039).

Two patients in each of the groups experienced at least one ocular adverse event. One patient in the Xalatan group withdrew early from the study due to drug intolerance (pruritus and burning sensation).

The percentage of patients satisfied with treatment was statistically significantly higher in the Monoprost group compared with the Xalatan group (59% versus 29%, *P* = 0.0009), and the percentage of patients reporting improvements in impact of treatment on work and daily activities (7% versus 0, *P* = 0.02) and on leisure activities (9% versus 0, *P* = 0.01) was statistically significantly higher in the Monoprost group.

Table 18: Summary of Baseline Characteristics

Permission to reuse table requested and reply not received. Please see Table 1 from Denis P, Monoprost French Study Group. Unpreserved latanoprost in the treatment of open-angle glaucoma and ocular hypertension. a multicenter, randomized, controlled study. J Fr Ophtalmol. 2016 Sep;39(7):622-30.

Table 19: Safety and Tolerability Outcomes

	Monoprost N = 130 Tolerance Set	Xalatan N = 53 Tolerance Set
Patients with conjunctival hyperemia score of 2 or 3 (Efron scale), %		
Baseline	53	40
Day 84	20	34
Change from baseline to day 84	–33	–6
Conjunctival hyperemia score in worse eye, mean (SD)		
Baseline	1.4 (0.8)	1.2 (0.9)
Day 84	0.9 (0.7)	1.1 (0.8)
P value for difference in change from baseline to day 84	0.0004	
Ocular symptom score, mean (SD)		
During instillation		
Baseline	2.9 (2.9)	2.5 (3.0)
Day 84	0.9 (1.3)	1.6 (2.3)
Change from baseline to day 84	–2.0 (2.7)	–0.9 (2.2)
P value for difference in change from baseline to day 84	0.0035	
Between instillations		
Baseline	2.7 (3.1)	1.6 (2.3)
Day 84	0.9 (1.5)	1.3 (2.2)
Change from baseline to day 84	–1.8 (2.8)	–0.3 (1.3)
P value for difference in change from baseline to day 84	0.0003	
Absolute change in % of patients with disturbing or very disturbing ocular symptoms		
During instillation		
Dryness	–11.2	–4.1

	Monoprost N = 130 Tolerance Set	Xalatan N = 53 Tolerance Set
Irritation/tingling/burning	–22.8	–8.2
Tearing	–9.6	–4.3
Foreign body sensation	–12.0	–8.3
Photophobia	–5.6	–2.1
Between instillations		
Dryness	–17.2	–4.1
Irritation/tingling/burning	–15.3	0.0
Itching	–8.8	0.0
Tearing	–5.6	0.0
Foreign body sensation	–7.2	–2.1
Photophobia	–5.6	0.0
Ocular adverse events, n (%)	2 (2)	2 (4)

SD = standard deviation.

Source: Denis et al.[9]

Table 20: Patient Questionnaire Outcomes at End of Study

	Monoprost N = 130 Tolerance Set	Xalatan N = 53 Tolerance Set
Very satisfied patients, %	59.4	29.4
P value for difference	0.0009	
Improvement in vision, % of patients	7.8	3.8
P value for difference	0.37	
Improvement in impact of treatment on daily/work activities, % of patients	6.9	0.0
P value for difference	0.020	
Improvement in impact of treatment on leisure activities, % of patients	9.2	0.0
P value for difference, % of patients	0.0097	
Improvement in sleep, % of patients	5.4	1.9
P value for difference	0.15	

Source: Denis et al.[9]

Discussion

The results demonstrated noninferiority in IOP-lowering efficacy of Monoprost compared with Xalatan over a three-month period. One of the inclusion criteria was that IOP had to be stable and no greater than 18 mm Hg (and both eyes treated for at least six months with preserved latanoprost 0.005% monotherapy); therefore, all of the patients were known to respond favourably to Xalatan.

Ocular signs and symptoms (including conjunctival hyperemia) and quality of life remained mostly constant between the two time points in the Xalatan group, which would be expected in a sample of patients who had already been on Xalatan for at least six months before the study. There were absolute decreases of 8% in the patients in the Xalatan group with irritation/tingling/burning and foreign body sensation upon instillation.

There was an absolute reduction of 33% in the proportion of patients on Monoprost with conjunctival hyperemia judged to be 2 or 3 on the Efron scale (possible scores of 0 to 4). However, the mean change in score was 0.5 and may not be clinically meaningful.

The mean ocular symptom score also decreased more in the Monoprost group than in the Xalatan group, with mean differences between the treatment groups of 1.1 and 1.5. This corresponds to one- to two-degree increases in severity for one ocular symptom.

Patients in the Monoprost group had greater reductions in patients with disturbing or very disturbing severity for all symptoms (absolute reductions of 5.6% to 22.8% with Monoprost versus reductions of up to 8.3% with Xalatan), although statistical analysis was not provided for these comparisons. For these magnitudes of change, the baseline percentages of patient with these symptoms would have been higher than those in the pivotal study, which were all 6% or less.[6] Possible reasons for these differences may be the higher proportion of patients in the phase IV study with glaucoma, differences in disease duration, and differences in medication history. However, duration of disease and IOP-lowering treatment in the manufacturer's studies are not available for comparison. Finally, only two patients in each group experienced an ocular adverse event.

When asked in a questionnaire about impacts on quality of life, less than 4% of patients in the Xalatan group reported improvements in any of the domains. More patients in the Monoprost group reported an improvement in work and daily activities as well as leisure activities; however, less than 10% reported improvements in each category. About twice the proportion of patients in the Monoprost group compared with the Xalatan group reported being satisfied with treatment (59% versus 29%).

Limitations

The main limitation of the study is that neither patients nor investigators were blinded to treatment allocation. While IOP could be measured objectively, all of the other outcomes relied on symptoms and quality of life reported by patients and on judgment of ocular signs by investigators. Knowledge of treatment and expectations of improved tolerability with Monoprost could have caused investigators and patients to overestimate signs and symptoms with Xalatan treatment and underestimate the same with Monoprost treatment. This would have overestimated the reduction of symptoms and improvement in treatment impact seen with Monoprost versus Xalatan.

There was a greater proportion of patients in the Xalatan group who had switched drugs within the five years before the study (43% for Xalatan versus 32% for Monoprost). As half of all patients who switched had done so due to local intolerance, these patients may have been more likely to report ocular symptoms during and between instillations. The imbalance between groups could have led to overestimation of the differential improvements in reported symptoms.

While conjunctival hyperemia showed a larger, statistically significant reduction in the Monoprost group versus the Xalatan group , the mean change in Efron scale score may not have been clinically meaningful. The same held for mean ocular symptom score during and between instillations. The decreases in proportion of patients experiencing disturbing or very disturbing ocular symptoms are potentially relevant, but statistics for comparisons were not reported. While patients viewed Monoprost favourably compared with Xalatan in terms of satisfaction and impact on quality of life, the study did not use a validated quality-of-life instrument, and there is no strong evidence that these results would have translated into

improved patient adherence to treatment. There was no attempt to measure patients' adherence to study treatment during the trial, either through recordkeeping or drug accountability.

Aside from the IOP end points, type I error rate was not controlled for, and statistical analysis of all other end points should be considered exploratory in nature.

The study design more closely resembles real-life use of antiglaucoma drugs than the previously conducted phase III RCTs. However, the study was conducted in France, potentially limiting generalizability to the Canadian setting.

Conclusion

This open-label, phase IV study comparing Monoprost with Xalatan in patients with open-angle glaucoma and ocular hypertension demonstrated noninferiority in IOP-lowering efficacy of Monoprost compared with Xalatan. On average, patients in the Monoprost group experienced fewer and/or less severe ocular symptoms and had less severe conjunctival hyperemia than those in the Xalatan group. However, knowledge of treatment assignment may have led to an overestimation of the improvements seen with Monoprost. Greater proportions of patients on Monoprost reported satisfaction with treatment and some quality-of-life improvements, although these outcomes were also prone to bias due to lack of blinding. Outcomes other than IOP were not adjusted for multiple comparisons and should be considered exploratory. The study did not measure patient adherence to study treatment.

Appendix 7: Summary of Indirect Comparisons

Introduction

The aim of this section is to assess indirect evidence for the efficacy and harms of Monoprost compared with any of the comparators listed in the CADTH Common Drug Review (CDR) systematic review protocol. The only relevant randomized clinical trials (RCTs) directly comparing Monoprost with other drugs have Xalatan as the comparator.

Methods

A literature search was undertaken to identify relevant published indirect comparisons involving Monoprost.

Description of Indirect Comparisons Identified

The only relevant study identified from the literature search was the indirect comparison used as the source of efficacy data for first-line therapy in the pharmacoeconomic analysis submitted by the manufacturer.

The study, sponsored by the manufacturer and conducted by Cucherat et al. in France,[10] is a meta-analysis of RCTs comparing the efficacy and safety of Monoprost with other prostaglandin analogues (PGAs: bimatoprost, travoprost, latanoprost, or tafluprost) for the treatment of open-angle glaucoma (OAG) or ocular hypertension. The corresponding internal report[44] was provided by the manufacturer upon request and is referred to in this appendix as the "manufacturer's report."

Review and Appraisal

Objectives and Rationale

Aside from one publication[7] based on the pivotal trial comparing Monoprost with preserved latanoprost, there are no publications comparing Monoprost with other relevant PGAs for the treatment of OAG and ocular hypertension. The objective of the review was to evaluate the efficacy (in lowering intraocular pressure [IOP]) and safety (related to hyperemia) of Monoprost monotherapy compared with monotherapy with other PGAs for the treatment of OAG and ocular hypertension using a network meta-analysis and indirect comparison approach.

Methods

Study Eligibility and Selection Process

The methods for study selection and the outcomes extracted were clearly defined and pre-specified. A search using disease and drug terms and filtering for RCT study design was conducted in MEDLINE, Embase, and the Cochrane Controlled Trials Register up to December 2011 without language or publication restrictions. Conference proceedings in the Web of Knowledge database were also searched to identify ongoing or unpublished studies. Citations in studies and review articles retrieved from the PubMed search were reviewed in addition to Medscape, the US FDA website, and drug manufacturer websites. Details on whether screening and data abstraction were performed by more than one

reviewer were not available in the manufacturer's report, although the publication stated that a second reviewer checked data for accuracy.

Studies were included if patients met reasonable criteria for a diagnosis of OAG or if they had ocular hypertension with a baseline IOP higher than 20 mm Hg. Patients had to be either treatment-naive or have undergone a washout period before randomization and could not be on medications that could affect IOP. They also must not have undergone an intraocular laser procedure or surgery in the three months before screening. RCTs (double-masked, single-masked, or open-label) were included if they were at least two months long and evaluated monotherapy with a commercially available PGA (studies with drugs withdrawn from the market worldwide were excluded).

A total of 21 RCTs were selected for inclusion in the systematic review, including five trials with three treatment arms. One of the RCTs was an unpublished comparison between two different formulations of bimatoprost and did not contribute to the meta-analyses because of a lack of data. A list of excluded studies and reasons for exclusion was provided in the manufacturer's report and the publication.[44]

CDR checked details from four of the included studies for accuracy, as reported in the systematic review.[45-48] Study design, sample size, baseline characteristics, follow-up duration, and treatments compared were accurately presented in all four studies. In one study, patients administered two drops of study drug in both eyes, contrary to the recommended dosages.[46] Since the systematic review protocol did not specify an IOP measurement technique, methods of measuring IOP varied. The following instruments were used: tonometer (type unspecified),[45] pulsatile ocular blood flow tonograph,[46] Goldmann tonometer,[47] and applanation tonometer (type unspecified).[48] Two of the four studies did not specify which eye or eyes were studied.[45,46]

Data Extraction

The study characteristics abstracted were inclusion criteria, treatment type, and duration of follow-up. In the publication, abstracted data also included baseline characteristics of enrolled patients and treatment dosages.

There was some variation in the study designs and populations of the included studies. All were parallel-groups studies, seven were double-masked, 11 were single-masked (usually the investigator or evaluator was masked), one was open-label, and one did not report this aspect of study design. All trials had a follow-up duration of three months or longer except one trial that had a follow-up period of two months. Nine trials had six months of follow-up, while four had at least 12 months of follow-up. There were multi-centre trials in Canada, the US, and Italy, as well as two trials spanning multiple countries. One US study included only African-American patients. Sample sizes ranged from 18 to 690 patients. Mean ages ranged from 47 to 68 years (age was not reported in two studies), while proportions of female patients ranged from 39% to 62%, except for one trial in which nearly 75% of patients were female.

In 15 of the studies, patients had either OAG or ocular hypertension, but two studies included a small percentage (< 10%) of patients with other types of glaucoma, two studies included only patients with OAG, and one study did not specify the type of glaucoma. Three studies specified that patients were treatment-naive, and two other studies were in newly diagnosed patients. The mean baseline IOP in treatment groups was similar among the trials, ranging from 22.9 mm Hg to 28.3 mm Hg (and from 24 mm Hg to 27 mm Hg for most).

For all treatment arms, administration was once a day and dosages had to comply with approved labelling, although no further details were provided on dosage. Information on time of administration and adherence to study drug were not reported.

A check for accuracy in a selection of the included studies revealed inaccuracies and deviations from the systematic review methods. Of the four studies examined, only one was accurate and compliant with the systematic review methods.[47] For one study comparing bimatoprost 0.03% and travoprost, only hyperemia was extracted, despite the availability of data on change in IOP at three months.[45] Hyperemia reporting in this study was based on patient reporting of adverse events rather than investigator observation.[45] Another study reported that all cases of hyperemia resolved spontaneously by three weeks of study treatment, suggesting that the outcome was inappropriately extracted.[46] Mean difference in IOP at three months was also extracted inaccurately from this study (–0.4 mm Hg was extracted instead of –0.1 mm Hg).[46] IOP results were extracted from a third study, which did not report values for the three-month time point and did not report morning values separately.[48] Therefore, it is not clear whether the IOP estimates were in accordance with the systematic review criteria.

Comparators

The comparators in the study included almost all of the PGAs currently marketed in Canada for the treatment of OAG and ocular hypertension, with the exception of the recently approved polyquaternium-1–preserved travoprost 0.003% (Izba). The relevant comparators were latanoprost 0.005%, bimatoprost 0.03%, bimatoprost 0.01%, and sofZia-preserved travoprost 0.004%. Polyquaternium-1–preserved travoprost 0.004%, travoprost 0.004%, and tafluprost 0.0015% were also included but are not marketed in Canada. Comparators were preserved with benzalkonium chloride (BAK) unless otherwise specified. SofZia- and polyquaternium-1–preserved travoprost were separate comparators in the publication[7] but were grouped together for the manufacturer's report.[44]

The report stated that one of the studies with travoprost used a concentration of 0.0015%, although concentrations were not consistently reported in the table showing characteristics of the interventions.

Outcomes

The efficacy outcomes to be reported were mean IOP after three months of treatment (if not available, mean IOP after two to six months was used with later time points favoured), mean IOP at the end of the study (if the follow-up period was two months to a year), and absolute and relative change in mean IOP from baseline to three months (if not available, the alternative time points from the first outcome were used). Only morning IOP was considered, although a rationale for this choice was not provided. Details on the methods used to measure IOP as well as lengths of washout periods were not provided. The publication included an exploratory noninferiority analysis of efficacy using a 1.5 mm Hg margin for the 95% confidence intervals (CIs).

The safety outcome was defined as conjunctival and/or ocular hyperemia (hyperemia or ocular redness) observed by the investigator at the three-month time point (or from two to six months if not available). Details on how hyperemia or ocular redness was defined were not provided.

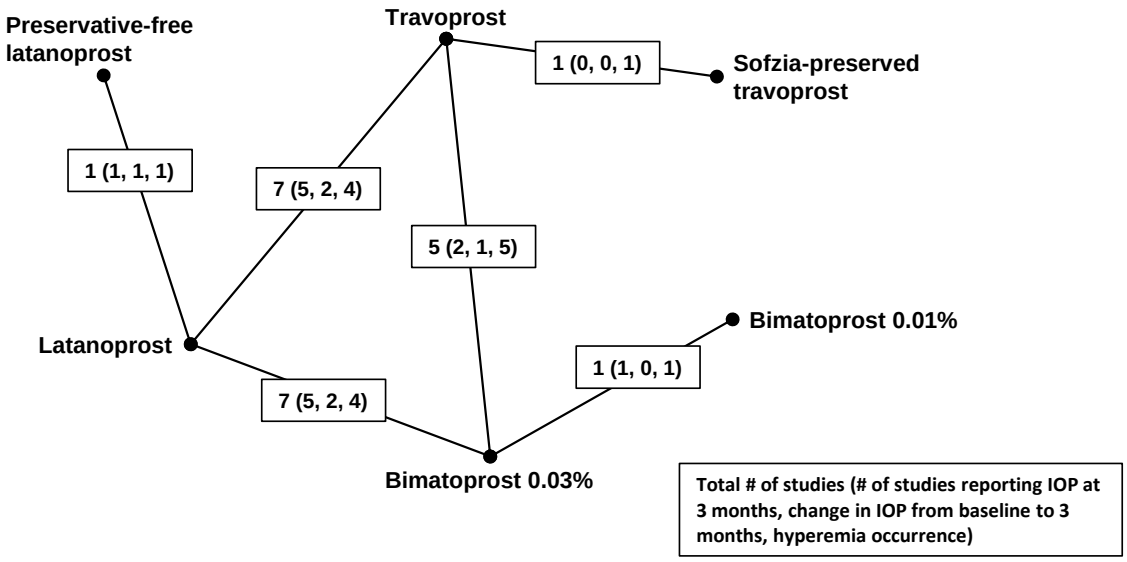
Quality Assessment of Included Studies

According to the manufacturer's report, studies were assessed for adequacy of allocation concealment, intention-to-treat (ITT) analysis, and blinding of outcome assessment. In the publication, studies were assessed for method of allocation concealment, randomization technique, double-blinding, and description of withdrawals and dropout. Formal quality assessment methods were not mentioned, and the results of these assessments were not provided. No studies were excluded on the basis of quality. According to the publication by Cucherat et al., publication bias was not assessed because of the small numbers of studies for each direct comparison.

Evidence Network

The evidence network (Figure 2) consisted mostly of studies comparing BAK-preserved latanoprost, bimatoprost 0.03%, and travoprost. Five studies contained treatment arms for each of these three comparators. Two additional studies compared latanoprost with travoprost, another two studies compared latanoprost with bimatoprost 0.03%, and another five studies compared travoprost and bimatoprost 0.03%. Only one study each was available for direct comparisons involving Monoprost or BAK-free latanoprost, bimatoprost 0.01%, and sofZia-preserved travoprost.

Figure 2: Evidence Network



Evidence network showing the number of studies available and the numbers of studies reporting each of the three outcomes for each pairwise comparison of relevant comparators.

Direct and Indirect Comparison Methods

The only direct comparison available for preservative-free latanoprost was the manufacturer-submitted pivotal trial, and it is therefore not summarized here. Indirect comparisons to the other PGAs were performed using the Bucher method.[49] It is assumed that the shortest path was used for each indirect comparison, as consistency within the closed loop among latanoprost, travoprost, and bimatoprost 0.03% was not assessed. The five trials with three treatment arms were analyzed as two separate two-way comparisons,

and only one comparison was retained if all three arms of one study were in the same meta-analysis. A method for choosing which comparison to keep was not described. All five of these trials compared latanoprost, travoprost, and bimatoprost 0.03%; avoiding the use of more than one comparison would have limited the data available for assessment of consistency.

Direct comparisons of outcomes reported by multiple studies were pooled using a fixed-effects model in the manufacturer's report and a random-effects model in the publication, without a rationale given for either. The pooled estimates were mean difference for mean IOP and mean IOP change, as well as odds ratio for occurrence of hyperemia. Hyperemia occurrence was based on the ITT set. Studies were weighted using inverse variance, and 95% CIs were computed for each pooled estimate.

In the absence of a reported mean value, the median was used, if available. According to the manufacturer's report, mean values were occasionally substituted with medians or extracted from graphs. Standard errors of differences were calculated as the sum of the variances of the individual values, regardless of whether the study design was crossover or parallel-groups. If the standard error was not reported, it was estimated using conservative *P* values, ranges, interquartile ranges, or graphs. Except for the estimation of standard error from a given range, details for these approaches were not reported or cited. If none of the methods could be used, standard deviation was imputed from the average standard deviation in the other studies.

Heterogeneity between studies was assessed using Cochran's chi-square test and the I^2 statistic. In cases where I^2 was 75% or greater, studies were combined using a random-effects model if they were clinically similar. Transitivity was not assessed between different comparisons. There was no mention of assessment of clinical similarity other than in the case of an I^2 statistic of 75% or greater.

Results

Not all of the RCTs for a given comparison reported the outcomes of interest. The only outcomes assessed were mean difference in IOP at three months, mean difference in the change in IOP from baseline to three months, and odds ratio of hyperemia occurrence. Mean IOP at the end of the study was not analyzed, and the publication did not include change in IOP from baseline to three months. Where there were multiple studies contributing to a direct comparison, the I^2 statistic did not exceed 75%, and the results from the fixed models were used (Table 21, Table 22, and Table 23).

Efficacy results were available for comparisons of preservative-free latanoprost with BAK-free travoprost, bimatoprost 0.03%, and bimatoprost 0.01% (Table 24). Although there was a trend of higher IOP with preservative-free latanoprost at three months, all of the 95% CIs of the estimates for IOP and change in IOP overlapped with 0. The 95% CIs for IOP at three months were within the 1.5 mm Hg equivalence margin defined in the publication's exploratory analysis, and mean differences at three months were less than 1 mm Hg. The greatest difference between treatments for pooled estimates of efficacy was in the reduction in IOP from baseline to three months between preservative-free latanoprost and bimatoprost 0.03%, which was 0.94 mm Hg in favour of bimatoprost 0.03%, although the 95% CI overlapped with 0 (–0.09 mm Hg to 1.94 mm Hg).

The upper bounds of the 95% CIs for the odds ratios of hyperemia occurrence were all less than 1, and mean odds ratios ranged from 0.18 to 0.52, suggesting lower occurrence of

hyperemia with preservative-free latanoprost versus all comparators (sofZia-preserved travoprost, bimatoprost 0.03%, and bimatoprost 0.01%).

In the manufacturer's report, the I^2 statistic was 0 for all but two direct comparisons, and the fixed-effects and random-effects model results were identical. For the two direct comparisons with some heterogeneity, the 95% CIs were wider with the random-effects model. However, the interpretation did not change, and the indirect comparisons available in both reports for IOP at three months were identical.

Table 21: Intraocular Pressure at Three Months — Direct Comparisons

Comparison	IOP at 3 Months, Mean Difference (95% CI)	I^2	Number of Studies
Bimatoprost 0.03% versus travoprost	–0.45 (–1.48 to 0.58)	0	2
Bimatoprost 0.03% versus latanoprost	–0.09 (–0.53 to 0.36)	0	5
Bimatoprost 0.01% versus bimatoprost 0.03%	0.30 (–0.32 to 0.92)	N/A	1
Preservative-free latanoprost versus latanoprost	0.40 (–0.02 to 0.82)	N/A	1
Travoprost versus latanoprost	0.15 (–0.40 to 0.70)	19%	5

CI = confidence interval; IOP = intraocular pressure; N/A = not applicable.

Note: Results from fixed-effects model are reported.

Source: Manufacturer-provided report.[44]

Table 22: Change in Intraocular Pressure at Three Months — Direct Comparisons

Comparison	Change in IOP From Baseline to 3 Months, Mean Difference (95% CI)	I^2	Number of Studies
Bimatoprost 0.03% versus travoprost	–0.40 (–2.44 to 1.64)	N/A	1
Bimatoprost 0.03% versus latanoprost	–0.54 (–1.13 to 0.05)	54%	2
Preservative-free latanoprost versus latanoprost	0.40 (–0.09 to 0.89)	N/A	1
Travoprost versus latanoprost	0.55 (–0.25 to 1.34)	0	2

CI = confidence interval; IOP = intraocular pressure; N/A = not applicable.

Note: Results from fixed-effects model are reported.

Source: Manufacturer-provided report.[44]

Table 23: Hyperemia or Ocular Redness at Three Months — Direct Comparisons

Comparison	Hyperemia Occurrence, OR (95% CI)	I^2	Number of Studies
Bimatoprost 0.03% versus travoprost	1.36 (0.85 to 2.18)	0	5
Bimatoprost 0.03% versus latanoprost	2.87 (2.11 to 3.92)	0	4
Bimatoprost 0.01% versus bimatoprost 0.03%	0.67 (0.43 to 1.04)	N/A	1
Preservative-free latanoprost versus latanoprost	0.52 (0.31 to 0.86)	N/A	1
Travoprost versus latanoprost	2.03 (1.50 to 2.76)	0	4

CI = confidence interval; N/A = not applicable; OR = odds ratio.

Note: Results from fixed-effects model are reported.

Source: Manufacturer-provided report.[44]

Table 24: Indirect Comparisons

Comparison	IOP at 3 Months, Mean Difference (95% CI)	Change in IOP From Baseline to 3 Months, Mean Difference (95% CI)	Hyperemia Occurrence at 3 Months, OR (95% CI)
Preservative-free latanoprost versus			
SofZia-preserved travoprost	N/A	N/A	0.37 (0.16 to 0.84)
Bimatoprost 0.03%	0.49 (–0.13 to 1.10)	0.94 (–0.06 to 1.94)	0.18 (0.10 to 0.33)
Bimatoprost 0.01%	0.19 (–0.69 to 1.06)	N/A	0.27 (0.13 to 0.56)

CI = confidence interval; IOP = intraocular pressure; N/A = not applicable; OR = odds ratio.

Source: Manufacturer-provided report[44] and Cucherat et al.[10]

Critical Appraisal

Strengths

The objectives of the study were clearly stated, and the meta-analysis was based on a systematic literature search of multiple databases with pre-specified study selection criteria and outcomes for extraction. The evidence network connects all of the comparators and includes all of the PGAs currently marketed in Canada, with the exception of the recently approved polyquaternium-1–preserved travoprost 0.003% (Izba). Results for sofZia-preserved travoprost were not available for the IOP outcomes. The outcomes of IOP and conjunctival hyperemia are both relevant, although there are other outcomes that would have been relevant to assessing safety.

The meta-analyses used the adjusted Bucher method (as opposed to naive comparisons). Direct and indirect comparisons were presented separately. Quality of the studies was assessed, although the details on this process were not provided. Heterogeneity among studies for each direct comparison was reported using the I^2 statistic. Effect estimates and 95% CIs were reported for individual studies.

Limitations

Some of the methods in the review were not described in detail, making it difficult to assess internal and external validity. Quality assessments of the individual studies were not provided and did not evaluate biases due to outcomes reporting, publication, or conflicts of interest. Details on the criteria for allocation concealment, ITT analysis, and blinding of outcome assessment were not provided. No studies were excluded on the basis of quality.

The IOP outcomes were relevant and defined in terms of time point. However, the methods for measuring IOP and determining presence of hyperemia or ocular redness were not specified, and the methods varied within the selection of studies checked for accuracy.[45-48] According to the clinical expert consulted for this review, lower baseline IOP is associated with a smaller reduction in IOP. If baseline IOP was not adjusted for in all studies, differences in baseline IOP distribution may have been sources of heterogeneity between studies. For hyperemia occurrence, at least two studies[45,46] relied on patient reporting rather than investigator observations, as specified in the protocol. Also, conjunctival hyperemia in the pivotal study[7] was assessed on the six-point McMonnies scale, and there is no clear method for converting the ordinal measure to a binary factor.

There were also issues with the planned statistical analyses. No rationale was provided for the use of odds ratios, rather than relative risk, for hyperemia. Instead of contacting authors of the individual studies for missing parameters, the analysts used medians when means were not reported and estimated standard deviations using a variety of methods when

these were not reported. If standard deviation could not be estimated from other descriptive statistics, it was imputed using the average from the other studies. The extent to which these methods were used and the effects they had on the pooled estimates is unknown.

The indirect comparisons between Monoprost and 0.01% bimatoprost and sofZia-preserved travoprost contained more than one intermediate comparator along the path. Additional intermediate comparators along a path may have contributed to greater between-comparisons heterogeneity. The impact of such heterogeneity could not be assessed because the consistency between different paths was not evaluated.

Fixed-effects models were used by default in the manufacturer's report without any rationale provided for their choice. Random-effects models were used in cases of 75% or greater heterogeneity, as long as the studies being pooled were clinically similar. The review author concluded that the studies were clinically similar based on the inclusion criteria and patient characteristics, as well as the fact that most of the studies were conducted for regulatory purposes and would have followed the same guidelines. However, there is no evidence reported to support these justifications. Random-effects models were therefore used by default in the publication, again, without any rationale provided.

There was variation in study design (masking of patients) and location, mean age of patients, proportion of female patients, and proportions of patients with OAG, other types of glaucoma, and ocular hypertension. However, these factors were not likely to bias the investigator-measured outcomes. The clinical expert consulted for this review indicated that age, sex, and disease stage (aside from baseline IOP) are not known to be associated with amount of IOP lowering. However, previous history of ocular symptoms related to use of PGAs may be associated with study observations of ocular symptoms. Studies with treatment-naive or newly diagnosed patients may report higher rates of hyperemia than studies with patients who tolerated treatment with PGAs for some time before baseline. Since the assessment of study dropout was not reported in the publication, it is not known whether early withdrawal of patients or poor compliance with treatment affected assessment of hyperemia in the ITT set.

Since all of the studies were assessed for clinical similarity as a whole, transitivity was assessed, as was homogeneity of studies within direct comparisons. Consistency between direct and indirect comparisons was not assessed, likely because of a lack of comparisons within the closed loop from independent studies.

Discussion

The results from the direct and indirect comparisons of Monoprost with bimatoprost 0.03% and bimatoprost 0.01% showed that Monoprost had IOP-lowering efficacy similar to that of the other PGAs. The 95% CIs for mean difference in IOP measured three months after study treatment were within a 1.5 mm Hg noninferiority margin. The 95% CIs for the mean differences in IOP at three months and IOP change from baseline to three months overlapped with 0, indicating lack of evidence for differences between the treatments. Given the similarity in efficacy between Monoprost and BAK-preserved latanoprost in the pivotal study,[6] these results were consistent with previous studies showing similar IOP-lowering efficacy among the PGAs, with the exception of greater efficacy of bimatoprost 0.03% in some cases.[11]

Since the manufacturer's report and publication were missing important details, it was difficult to assess the robustness of the results. Details and results of the quality

assessment for the included studies were not provided, and consistency between direct and indirect comparisons was not assessed. Given the lack of strong evidence for known confounders for IOP lowering other than baseline IOP, clinical similarity between the studies for the efficacy outcomes may have been justified. IOP measurements are objective and do not suffer from bias in single-masked trials. However, the instruments used to measure IOP and statistical methods used to estimate differences in IOP were not specified, and these could be sources of heterogeneity in the pooled results.

The pooled odds ratios and 95% CIs for hyperemia or ocular redness after three months of study treatment were less than 1 for the indirect comparisons of Monoprost with bimatoprost 0.03%, bimatoprost 0.01%, and sofZia-preserved travoprost, indicating lower proportions of patients with hyperemia or ocular redness with Monoprost treatment.

The pooled estimates for hyperemia or ocular redness were more vulnerable to bias than the estimates for IOP. Hyperemia was not clearly defined and was observed by the investigator after three months of study treatment. However, examination of a sample of studies revealed at least two studies that used patient-reported hyperemia, with one of the studies reporting that conjunctival hyperemia resolved after three weeks of study treatment. Definitions of hyperemia and ocular redness varied among studies, with some studies assessing hyperemia on a scale and others using adverse event reporting. Combining these results was likely inappropriate despite the use of odds ratios.

Other limitations contributing to uncertainty of the pooled estimates were the use of a variety of methods to deal with missing parameters and the lack of assessment of biases due to outcomes reporting, publication, or conflicts of interest.

Conclusion

Direct or indirect comparisons were performed for Monoprost versus several comparators relevant in the Canadian setting. However, the only available closed loop was among the three most common PGAs: BAK-preserved latanoprost, bimatoprost, and travoprost. Since several studies were designed with three arms, there was insufficient independent data for the assessment of consistency between different pathways in the evidence network. Also, the pivotal study was the only study to feature a direct comparison with Monoprost.

The results suggest that Monoprost is noninferior to bimatoprost 0.03% and bimatoprost 0.01% in terms of IOP-lowering efficacy and superior to sofZia-preserved travoprost and both forms of bimatoprost in terms of reducing hyperemia (i.e., ocular redness); however, there are significant limitations contributing to uncertainty in the estimates. Sources of uncertainty include lack of information on quality assessment of individual studies, methods used to derive individual study estimates, differences in instruments used to measure IOP, varying definitions of hyperemia, potential bias in hyperemia assessments, and concerns with the accuracy of data extraction from the individual studies. Pooling of hyperemia results across studies was likely inappropriate.

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