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CADTH COMMON DRUG REVIEW

Clinical Review Report

TRAVOPROST 0.00 3% (IZBA)

(Novartis Pharmaceuticals Canada Inc. on behalf of Alcon Canada Inc.)

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

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Table of Contents

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Abbreviations

AE	adverse event
BAC	benzalkonium chloride
BCVA	best corrected visual acuity
CI	confidence interval
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GAT	Goldmann applanation tonometry
IOP	intraocular pressure
ITT	intention-to-treat
OAG	open-angle glaucoma
PP	per-protocol
PQ	polyquaternium-1
RCT	randomized controlled trial

Drug	travoprost 0.003% ophthalmic solution (Izba)
Indication	The reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
Listing Request	As per indication
Dosage form(s)	Topical ophthalmic solution — one drop in the affected eye(s) once daily.
NOC date	23-09-2016
Manufacturer	Novartis Pharmaceuticals Canada, Inc. on behalf of Alcon Canada Inc.

Executive Summary

Introduction

Glaucoma is an eye disease characterized by progressive optic nerve damage that leads to gradual visual field loss; it can eventually result in blindness. Glaucoma is usually associated with elevated intraocular pressure (IOP), which is considered a major risk factor for disease progression. The most common form of glaucoma is open-angle glaucoma (OAG).

Izba (Travoprost 0.003% PQ) is an eye-drop solution that contains 30 mcg of travoprost per millilitre of solution and is preserved with polyquaternium-1 (POLYQUAD [PQ]). It has the same therapeutic indication, contains reduced concentration of active substance, and has different preservative than the travoprost 0.004% solutions marketed in Canada. Travoprost, a prostaglandin analogue, is used to decrease elevated IOP in patients with OAG or ocular hypertension.

The objective of the review was to identify, summarize, and critically assess the beneficial and harmful effects of travoprost 0.003% PQ for the treatment of elevated IOP in patients with ocular hypertension or OAG.

Results and Interpretation

Included Studies

One randomized controlled multi-centre study (Study C-11-034) was identified to support the efficacy and safety of travoprost 0.003% PQ. In the study, patients were randomly assigned (1:1) to travoprost 0.003% PQ (n = 442) or travoprost 0.004% preserved with benzalkonium chloride (BAC) (n = 422). Both medicines were given as one drop in the affected eye once a day, in the evening, for a period of three months. The primary objective of this study was to demonstrate that the IOP-lowering efficacy of travoprost 0.003% PQ is equivalent to travoprost 0.004% BAC in patients with OAG or ocular hypertension.

The primary efficacy end point in the study was the mean IOP (in millimetres of mercury [mm Hg]). IOP is considered a surrogate outcome. However, there is considerable evidence associating IOP with the progression of glaucoma, and lowering IOP is considered the only clinically validated approach to treating glaucoma. In the study, treatment outcomes were assessed during three on-therapy study visits (week 2, week 6, and month 3) and at three assessment time points (8 a.m., 10 a.m., and 4 p.m.).

Equivalence was concluded if the two-sided 95% confidence interval for the difference in mean IOP (travoprost 0.003% PQ group minus travoprost 0.004% BAC group) was within 1.5 mm Hg at each of the three time points (8 a.m., 10 a.m., and 4 p.m.) for each on-therapy visit (week 2, week 6, and month 3). As well, a more stringent equivalence margin of ± 1.0 mm Hg was used in the equivalence testing. Justification for the equivalence margin was not provided in the submission. However, the equivalence margin was recommended by the FDA clinical review team; as well, the clinical expert consulted on this review indicated that it is a suitable margin to show clinical equivalence.

The key limitation of Study C-11-034 is that equivalence was determined versus BAC-preserved travoprost 0.004% instead of versus the sofZia-preserved travoprost 0.004% formulation available in Canada. BAC preservative has been associated with tolerability issues and seems to increase the incidence of hyperemia. In addition, the study provided no outcomes related to mobility, quality of life, topical medication use, or compliance/adherence.

Efficacy

The study showed that travoprost 0.003% PQ was as effective as travoprost 0.004% BAC in reducing pressure in the eye. In patients taking travoprost 0.003% PQ, the average eye pressure (measured at 8 a.m. in the morning) was 19.4 mm Hg, 19.3 mm Hg, and 19.2 mm Hg following two weeks, six weeks, and three months of treatment, respectively. The results matched the pressure seen at similar time points in patients taking travoprost 0.004% BAC (19.5 mm Hg, 19.3 mm Hg, and 19.3 mm Hg). All IOP mean differences were within the defined equivalence margins (both ± 1.5 mm Hg and ± 1.0 mm Hg margins) at all three assessment time points (8 a.m., 10 a.m., and 4 p.m.) during all three on-therapy study visits (week 2, week 6, and month 3).

Both groups of patients had similar best corrected visual acuity scores throughout the study, and the majority of patients in both arms had no change in the best corrected visual acuity score from baseline. Other efficacy outcomes defined in this review protocol were not reported in this submission.

Harms

The safety profiles of travoprost 0.003% PQ and travoprost 0.004% BAC were similar in the study. The most common adverse event reported during the study was hyperemia of the eye (ocular or conjunctival). A lower incidence of hyperemia was observed in travoprost 0.003% PQ group than in travoprost 0.004% BAC group (ocular hyperemia: 7.0% versus 8.1% and conjunctival hyperemia: 5.7% versus 7.1%, respectively). No serious adverse events related to study drug were reported. Three patients from the travoprost 0.003% PQ group and four patients from the travoprost 0.004% BAC group withdrew from the study due to adverse events. No patient deaths were reported in the study.

Conclusions

Travoprost 0.003% PQ appears similarly efficacious and safe compared with travoprost 0.004% BAC, although data on patient-reported outcomes are not available from the trial included in this review. In addition, evidence concerning the comparative efficacy and safety of travoprost 0.003% PQ and other IOP-lowering therapies is lacking.

In study C-11-034, travoprost 0.003% PQ provided IOP-lowering efficacy equivalent to that of travoprost 0.004% BAC in the treatment of patients with ocular hypertension or OAG. The adverse events reported in the study were local ocular effects consistent with the known safety profile of travoprost. The most common adverse event reported was hyperemia of the eye (ocular or conjunctival). However, the comparator used in this trial had a different preservative than that currently available in the Canadian market (Travoprost 0.004% Z, preserved with sofZia). Because formulations preserved with BAC have been associated with a higher incidence of hyperemia than formulations preserved with sofZia or PQ, we are not certain whether the safety profile seen with travoprost 0.003% PQ would be similar to that of travoprost 0.004% Z, used in Canada. However, the travoprost 0.003% PQ solution is identical to the formulation of travoprost 0.004% PQ marketed in Europe, with the exception of a lower concentration of the active substance, travoprost. The European Medicines Agency has concluded that no unexpected safety issues were identified when comparing travoprost 0.003% PQ and historical adverse events data for travoprost 0.004% (preserved with BAC, sofZia, or PQ).

Table 1: Summary of Results

Outcome	Study C-11-034				
	Travoprost 0.003% PQ		Travoprost 0.004% BAC		
On-Therapy Intraocular Pressure (ITT Population)					
	N (%)	mm Hg	N (%)	mm Hg	Mean difference (95% CI)
Baseline, mean (SD)					
8 a.m.	442 (100)	26.9 (2.5)	418 (100)	27.1 (2.9)	NR
10 a.m.	442 (100)	25.4 (2.8)	418 (100)	25.6 (3.2)	NR
4 p.m.	442 (100)	24.6 (2.9)	418 (100)	24.8 (3.2)	NR
Week 2, mean ± SE					
8 a.m.	442 (100)	19.4 ± 0.16	416 (98.6)	19.5 ± 0.17	–0.1 (–0.5 to 0.3)
10 a.m.	442 (100)	18.6 ± 0.16	416 (98.6)	18.6 ± 0.16	0.0 (–0.4 to 0.4)
4 p.m.	442 (100)	18.0 ± 0.16	416 (98.6)	18.3 ± 0.16	–0.3 (–0.7 to 0.1)
Week 6, mean ± SE					
8 a.m.	439 (99.3)	19.3 ± 0.16	413 (97.9)	19.3 ± 0.17	0.0 (–0.4 to 0.4)
10 a.m.	440 (99.5)	18.5 ± 0.16	413 (97.9)	18.6 ± 0.17	–0.1 (–0.5 to 0.3)
4 p.m.	440 (99.5)	18.0 ± 0.16	413 (97.9)	18.1 ± 0.17	–0.2 (–0.6 to 0.2)
Month 3, mean ± SE					
8 a.m.	432 (97.7)	19.2 ± 0.17	408 (96.7)	19.3 ± 0.18	–0.1 (–0.5 to 0.3)
10 a.m.	432 (97.7)	18.3 ± 0.17	408 (96.7)	18.6 ± 0.18	–0.3 (–0.7 to 0.1)
4 p.m.	431 (97.5)	18.0 ± 0.16	408 (96.7)	18.0 ± 0.17	0.0 (–0.4 to 0.4)
Best Corrected Visual Acuity (Safety Population)					
[redacted]					
SAEs, Treatment-Related (Subjects With > 0 SAEs)					
n (%)	0		0		
SAEs, Not Treatment-Related (Subjects With > 0 SAEs)					
n (%)	5 (1.1)		7 (1.7)		
WDAEs					
n (%)	3 (0.7)		4 (1.0)		
Ocular hyperemia					
[redacted]					
Conjunctival hyperemia					
n (%)	25 (5.7)		30 (7.1)		
Dry eye					
[redacted]					
Eye pruritus					
[redacted]					
Eye irritation					
[redacted]					
Photophobia					
[redacted]					

BAC = benzalkonium chloride; CI = confidence interval; ITT = intention-to-treat; NR = not reported; PQ = polyquaternium-1; SAE = serious adverse event; SD = standard deviation; SE = standard error; WDAE = withdrawals due to adverse events.

Source: Peace et al. 2015,[1] clinical study report.[2]

Introduction

Glaucoma is a group of eye disorders affecting the optic nerve (i.e., glaucomatous optic neuropathy). In glaucoma, optic nerve fibres are progressively lost, and the optic disk changes shape. This, in turn, leads to irreversible loss of visual field and can eventually cause total blindness. Severity of glaucoma is categorized, based on the extent of optic nerve damage and visual acuity, into four stages: suspect, early, moderate, and advanced.[3] If left untreated, the peripheral visual field is the first to be lost; in more severe cases, patients develop tunnel vision.

In the presence of optic disk damage, glaucoma is commonly classified as open-angle or closed-angle glaucoma, based on the patency of the iridocorneal drainage angle (i.e., obstructed angle defines closed-angle glaucoma, as opposed to open-angle glaucoma [OAG] with nonobstructed angle).[3] Literature indicates that OAG has a higher prevalence and is more common than closed-angle glaucoma.[4,5]

The diagnosis of glaucoma is based on the patient‘s history and a comprehensive eye examination, including best corrected visual acuity (BCVA), pupillary reaction, automated perimetry, slit-lamp examination, intraocular pressure (IOP) measurements, central corneal thickness, gonioscopy, and dilated examinations.[3]

IOP, the fluid pressure inside the eye, is associated with the development and progression of glaucoma.[6-8] The glaucoma clinical practice guidelines published by the Canadian Ophthalmological Society report that lowering IOP is the only clinically established method of glaucoma treatment.[3] The guidelines recommend assigning an IOP upper threshold as a goal of therapy based on the severity of glaucoma, as follows:

- suspect, in which 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 longevity, quality of life, and risk factors for progression.[3]

Large differences in the rate of visual function loss have been reported among glaucoma patients and different glaucoma types. Based on progression rates from an untreated patient cohort (n = 118) in a six-year follow-up study (Early Manifest Glaucoma Trial), the mean time from full field of vision to blindness was estimated to be 25 years.[9] However, the respective median estimate was 70 years, indicating that the estimates above 25 years are more frequent and that the variation among patients is large.

A retrospective chart review from Sweden included 592 glaucoma patients who died between January 2006 and June 2010. In that cohort, the median time with a glaucoma diagnosis was 12 years (range from less than one year to 29 years). The cumulative incidences of blindness in at least one eye were 26.5% after 10 years and 38.1% after 20 years from diagnosis. The respective proportions for bilateral blindness were 5.5% and 13.5%.[10]

Disease Prevalence and Incidence

The global prevalence of primary OAG in adults aged 40 to 80 years is estimated to be 3.5% worldwide and 3.3% in in North America in 2013.[5]

In 2009, the Canadian Community Health Survey reported that an estimated 456,533 Canadians have a diagnosis of glaucoma.[11] Previously, based on data from five national surveys, an estimated 409,000 Canadians were reported to have been diagnosed with glaucoma in 2002-2003; with an estimated prevalence of 2.7% among those aged 40 years and older and 11% among those 80 years and older.[12] Neither publication provided the proportion of those with OAG. The overall number of patients with glaucoma is expected to increase as population age increases.[5,12]

Standards of Therapy

The primary aim of therapy is to lower IOP in order to prevent progressive vision loss and to maintain or enhance overall quality of life. The treatment strategies include topical ophthalmic drugs, laser therapy, and surgery. Pharmacologic therapy is the most common method of lowering IOP, and it is typically chosen as a first-line treatment.[3]

The topical ophthalmic drugs used for the reduction of elevated IOP in patients with OAG or ocular hypertension include:

- prostaglandin analogues (latanoprost, travoprost, and bimatoprost)
- beta blockers (betaxolol, levobunolol, timolol)
- alpha-2 adrenergic agonists (apraclonidine, brimonidine)
- carbonic anhydrase inhibitors (brinzolamide, dorzolamide)
- cholinergic drugs (pilocarpine)
- combination therapies (timolol/dorzolamide, timolol/brimonidine, timolol/latanoprost, timolol/travoprost, timolol/brinzolamide).

According to the clinical practice guidelines published by the Canadian Ophthalmological Society, prostaglandin analogues or beta adrenergic antagonists are typically used as a first-line pharmacologic therapy.[3] Prostaglandin analogues are often preferred as initial therapy, since they are most effective at lowering IOP.[3,13,14] However, other considerations such as cost, side effects, and intolerance are taken into account. If a patient does not response to initial therapy, alternative therapies or combination therapy may be considered.[13]

Patients with OAG need lifetime therapy. Because the disease is asymptomatic and the use of medicines may be inconvenient and cause adverse effects, compliance with OAG therapy is often poor.[13]

Drug

Izba is an eye-drop solution containing 30 mcg travoprost per millilitre of solution (travoprost 0.003%), preserved with polyquaternium-1 (POLYQUAD [PQ]).[15] The dose of travoprost is one drop in the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening. Travoprost is prostaglandin analogue, and it is used to decrease elevated IOP in patients with OAG or ocular hypertension.

Travoprost 0.003% PQ has the same therapeutic indication and contains the same active substance as the original 0.004% travoprost formulations, but it contains 25% less of active substance (Table 2).

Travoprost 0.004% solutions (both the original and generic products) marketed in Canada are preserved with sofZia (hereafter referred to as travoprost 0.004% Z).[16] The travoprost 0.004% solution that was first made available in Canada in 2001 was preserved with benzalkonium chloride (BAC). BAC has been associated with tolerability issues and, for that reason, two BAC-free travoprost formulations have been introduced: travoprost 0.004% Z and travoprost 0.004% preserved with PQ. Travoprost 0.004% Z received a Health Canada notice of compliance in 2009. Currently, travoprost 0.004% solutions preserved with BAC or PQ are not marketed in Canada. Travoprost 0.004% PQ was approved by the European Medicines Agency (EMA) in 2010.[17]

According to the manufacturer, the proposed rationale for travoprost 0.003% PQ is to provide patients with an alternative prostaglandin analogue option with a reduced concentration of travoprost and a better tolerated preservative, to improve overall drug safety.[17]

Table 2: Key Characteristics of Prostaglandin Analogues

	Travoprost 0.003% PQ	Travoprost 0.004% Z	Latanoprost	Bimatoprost
Mechanism of Action	PGA Prostaglandins increase the flow of fluid out of the eye. This helps to reduce the pressure inside the eye.			
Indication[a]	For the reduction of elevated IOP in patients with OAG or ocular hypertension	For the reduction of IOP in adult patients with OAG or ocular hypertension	For the reduction of IOP in patients with OAG or ocular hypertension. May be used for the reduction of IOP in patients with chronic angle-closure glaucoma who underwent peripheral iridotomy or laser iridoplasty	For the reduction of elevated IOP in patients with OAG or ocular hypertension
Route of Administration	Ophthalmic (topical)			
Recommended Dose	One drop in the affected eye(s) once daily in the evening			
Serious Side Effects / Safety Issues	Macular edema, iris darkening (hyperpigmentation), and skin darkening around the eye have been reported during treatment with PGAs. PGAs can also change length, thickness, pigmentation, or number of eye lashes. PGAs should be used with caution in patients with a history of iritis/uveitis or herpetic keratitis. Contact lenses should be removed before administration; lenses may be reinserted 15 minutes after administration.			

[a] Health Canada indication.

IOP = intraocular pressure; OAG = open-angle glaucoma; PGA = prostaglandin analogue; PQ = polyquaternium-1; Z = sofZia.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of travoprost 0.003% PQ for the treatment of elevated intraocular pressure in patients with ocular hypertension or OAG.

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
Intervention	Travoprost 0.003% ophthalmic solution (Izba)
Comparators	**Topical ophthalmic medications** • Prostaglandin analogues (including travoprost 0.004%) • Beta blockers • Carbonic anhydrase inhibitors • Alpha-2 adrenergic agonists • Direct-acting cholinergic agonists • Combination therapies (timolol/dorzolamide, timolol/brimonidine, timolol/latanaprost, timolol/travoprost, timolol/brinzolamide)
Outcomes	**Key efficacy outcomes:** • Intraocular pressure • Visual field loss • Function (e.g., Visual Activity Questionnaire, Glaucoma Symptom Identifier) • Mobility • Quality of life (e.g., Glaucoma Health Perception Index) **Other efficacy outcomes:** • Topical medication use • Compliance/adherence/persistence **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms (hyperemia, dry eye, blurred vision, photophobia, ocular pruritus, ocular irritation; rare harms: swelling of macula, iritis, herpes simplex activation)
Study Design	Published and unpublished phase III RCTs (both DB and open-label)

AE = adverse events; DB = double-blind; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse event.

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled

vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Izba and travoprost.

Methodological filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 28, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on July 19, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.
In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Results

Findings from the Literature

A total of three reports presenting data for one study were identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

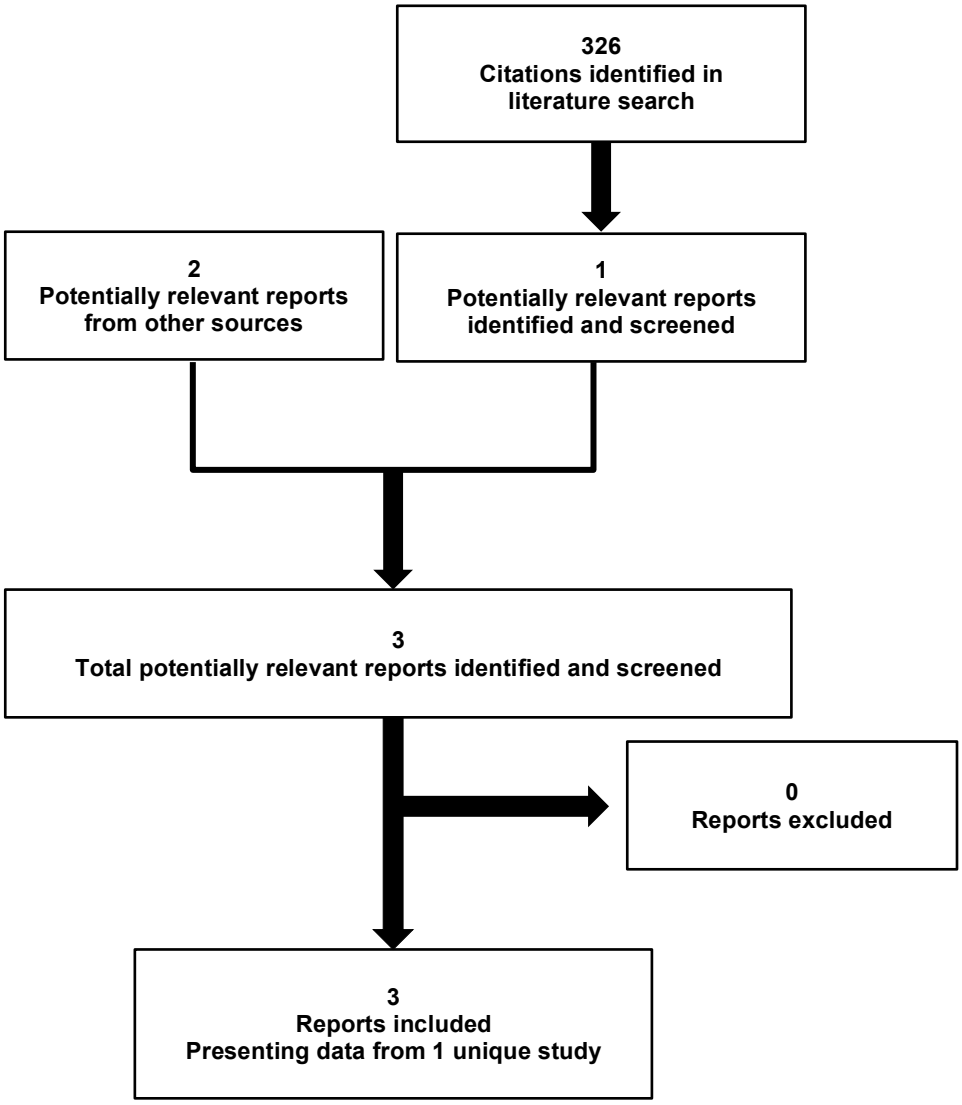


Table 4: Details of Included Study

		Study C-11-034
Designs and Populations	**Study Design**	Phase III, double-masked, RCT, equivalence trial
	Locations	US, Western Europe
	Randomized (N)	864
	Inclusion Criteria	• Patients with open-angle glaucoma (OAG) or ocular hypertension • Age ≥ 18 years • Mean IOP (in two eligibility visits) in at least 1 eye (the same eye) ≥ 24 mm Hg at the 8 a.m. time point, and ≥ 21 mm Hg at both the 10 a.m. and 4 a.m. time points • Mean IOP ≤ 36 mm Hg at all time points in both eyes
	Exclusion Criteria	• Modified Shaffer angle grade < 2 in either eye • Cup-to-disk ratio > 0.8 • Severe central visual field loss in either eye • Chronic, recurrent, or severe inflammatory eye disease • Intraocular surgery or ocular trauma within the previous 6 months • Ocular infection or inflammation or ocular laser surgery within the previous 3 months • Central corneal thickness > 620 µm • BCVA score worse than 55 ETDRS letters • Clinically significant or progressive retinal disease or other severe ocular pathology • Hypersensitivity to prostaglandin analogues • Any abnormality preventing applanation tonometry in either eye • Patients who, in opinion of the investigator, were unable to discontinue all IOP-lowering ocular medications before the study • Use of any additional topical or systemic ocular hypotensive medication during the study • Concurrent use of glucocorticoids administered by any route; use of glucocorticoids during the study and for at least 4 weeks (chronic use) or at least 2 weeks (in case of intermittent use) prior to the eligibility 1 visit • Less than 30 days' stable dosage regimen before the screening visit of any medications (excluding the IOP-lowering treatments) or substances administered by any route and used on a chronic basis that may have affected IOP (i.e., beta adrenergic blocking agents) • No change in dose/regimen of chronic medications used during study • Therapy with another investigational agent within 30 days prior to the screening visit
Drugs	**Intervention**	Polyquaternium-1 (PQ)–preserved travoprost 0.003% 1 drop in the treated eye(s) once daily at 8 p.m. for 3 months
	Comparator(s)	Benzalkonium chloride (BAC)–preserved travoprost 0.004% 1 drop in the treated eye(s) once daily at 8 p.m. for 3 months
Duration	**Phase**	
	Run-in	Up to 35 days (1 screening and 2 eligibility visits)
	Double-blind	3 months
	Follow-up	Not applicable
Outcomes	**Primary End Point**	Mean IOP at week 2, week 6, and month 3, measured for each assessment time point (8 a.m., 10 a.m., and 4 p.m.)
	Other End Points	• Mean change from baseline in IOP • Per cent change from baseline in IOP • Percentage of patients with IOP level < 18 mm Hg • Percentage of patients who achieved ≥ 30% IOP reduction from baseline

		Study C-11-034
		• Trial-associated safety end points
Notes	**Publications**	Peace et al. 2015[1]

BAC = benzalkonium chloride; BCVA = best corrected visual acuity; EMA = European Medicines Agency; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; PQ = polyquaternium-1; RCT = randomized controlled trial.

Source: Peace et al. 2015,[1] clinical study report,[2] Health Canada reviewer's report: Izba,[18] European public assessment report from EMA,[19] and FDA drug-approval package.[20]

Included Studies

Description of Studies

One randomized controlled trial (Table 4) met the inclusion criteria.[1] The primary objective of this study (Study C-11-034) was to demonstrate that the IOP-lowering efficacy of travoprost 0.003% PQ is equivalent to travoprost 0.004% BAC in patients with OAG or ocular hypertension.

The study was conducted in two stages (Table 5). The first stage included a screening visit and two eligibility visits. The second stage included three on-therapy follow-up visits. At screening, patients discontinued all other IOP-lowering ocular medications. The first eligibility visit was scheduled after a predetermined washout period according to the patient's pre-study medication. The specified washout period varied for different drug types.

Table 5: Study Plan

Stage 1 (Screening / Eligibility)								Randomization	Stage 2 (Treatment)								
Study visit	**Screen**	**Eligibility 1 (scheduled based on washout[a])**			**Eligibility 2 (3–8 days from Eligibility 1)**				**Week 2 (14 ± 1 days)**			**Week 6 (42 ± 3 days)**			**Month 3 (90 ± 3 days)**		
Assessment time point		8 a.m.	10 a.m.	4 p.m.	8 a.m.	10 a.m.	4 p.m.		8 a.m.	10 a.m.	4 p.m.	8 a.m.	10 a.m.	4 p.m.	8 a.m.	10 a.m.	4 p.m.

[a] Duration of washout period: miotics and oral/topical carbonic anhydrase inhibitors ≥ 4 days; alpha and alpha/beta agonists ≥ 13 days; beta agonists, prostaglandin analogues, and combination drugs ≥ 27 days.

Source: Clinical study report.[2]

Patients were randomly assigned (1:1) to travoprost 0.003% PQ or travoprost 0.004% BAC at the second eligibility visit. Randomization was accomplished using an interactive Web response system. Randomization was stratified, within the investigational centre, according to the 8 a.m. baseline IOP (low: 24 mm Hg to 27 mm Hg; high: 28 mm Hg to 36 mm Hg). The on-therapy study visits were scheduled 14 days (week 2), 42 days (week 6), and 90 days (month 3) after the second eligibility visit. Based on the description of the randomization method provided, it is unclear whether the randomization occurred at each individual site or centrally.

The study was double-masked, meaning that the patients, the investigators, the investigational centre staff, the sponsor, and the clinical monitors were not aware of the individual patient's treatment assignment. As well, the external packaging of the study products was identical.

Populations

Inclusion and Exclusion Criteria

Patients recruited for the study had to go through a screening visit during which they were assessed for inclusion and exclusion criteria. The screening visit included assessment of BCVA, slit-lamp evaluation, examination of the iridocorneal angle, visual field function tests, IOP measurements, dilated fundus examinations, and central corneal thickness. Patients with a diagnosis of OAG or ocular hypertension were included in the study, provided they met the inclusion and exclusion criteria reported in Table 4. The criteria used in the diagnosis of OAG were not specified in the submission. To meet the specified IOP range, patients underwent two eligibility visits; in each visit, the mean IOP had to be in the range of 24 mm Hg to 36 mm Hg, inclusive, at 8 a.m., then in the range of 21 mm Hg to 36 mm Hg, inclusive, at 10 a.m., and again at 4 p.m. According to the clinical expert, the study eligibility criteria are acceptable and consistent with those applied previously in the clinical trials for IOP-lowering ophthalmic medications. Only one eye from each patient was chosen as the study eye, usually the worse one; if both were equal in all IOP measurements, then the right eye was chosen as the study eye.

Baseline Characteristics

The baseline characteristics of the study population are reported in Table 6. The majority of patients were 65 years of age and older (56%; overall mean age = 65.2 years) and female (60%). A substantial proportion of the patients were black/African-American (25%). A majority of the patients had a diagnosis of OAG (69%). No clinically meaningful differences in the baseline characteristics were observed between study groups.

At screening, patients discontinued all other IOP-lowering ocular medications. No information on these pre-study medications (e.g., proportion of patients treated versus untreated) was reported.

Table 6: Summary of Baseline Characteristics, Intention-to-Treat Population

	Travoprost 0.003% PQ (n = 442)	Travoprost 0.004% BAC (n = 418)
Age, years		
Mean ± SD	65.4 ± 10.5	65.0 ± 10.9
< 65, n (%)	189 (42.8)	191 (45.7)
> 65, n (%)	253 (57.2)	227 (54.3)
Male, %	173 (39.1)	174 (41.6)
Race, n (%)		
White	316 (71.5)	307 (73.4)
Black	112 (25.3)	106 (25.4)
Asian	11 (2.5)	4 (1.0)
Other	3 (0.7)	1 (0.2)
Diagnosis, n (%)		
Ocular hypertension	130 (29.4)	121 (28.9)
OAG	304 (68.8)	290 (69.4)
OAG with pigment dispersion	7 (1.6)	7 (1.7)
OAG with pseudo-exfoliation	1 (0.2)	0 (0.0)
Baseline IOP, mm Hg		

Mean ± SD (8 a.m.)	26.9 ± 2.5	27.1 ±2.9
Mean ± SD (10 a.m.)	25.4 ± 2.8	25.6 ± 3.2
Mean ± SD (4 p.m.)	24.6 ± 2.9	24.8 ± 3.2
24 mm Hg to 27 mm Hg, n (%)	303 (68.6)	291 (69.6)
28 mm Hg to 36 mm Hg, n (%)	139 (31.4)	127 (30.4)
Corneal thickness, µm		
Mean ± SD	552.9 ± 35.0	551.8 ± 32.1

BAC = benzalkonium chloride; IOP = intraocular pressure; OAG = open-angle hypertension; PQ = polyquaternium-1; SD = standard deviation.

Source: Peace et al. 2015[1] and clinical study report.[2]

Interventions

A new formulation of travoprost 0.003% solution preserved with PQ was compared with travoprost 0.004% solution preserved with BAC.

The dose of either treatment (travoprost 0.003% PQ or travoprost 0.004% BAC) was one drop in each eye, once daily at 8 p.m. (± 30 minutes). Patients administered their first dose on the night of the eligibility 2 visit. The last dose was administered on the night before the three-month visit. The study drug was used in both eyes unless the investigator considered that administration in both eyes would pose a potential safety issue to the patient.

The external packaging of the study products was identical. In addition, the patients, the investigators, the investigational centre staff, the sponsor, and the clinical monitors were not aware of the treatment assigned to the individual study patients.

The use of all other IOP-lowering ocular medications was prohibited during the study. All patients who used these medications were required to undergo a washout period between the screening and eligibility 1 visits, as described in Table 5. In addition, patients were not allowed to use glucocorticoids administered by any route during the study. As well, there were requirements concerning medications that could have affected IOP (e.g., beta adrenergic blocking agents) and that were intended for chronic use. If patients had used these for less than 30 days, they were prohibited during the study. If patients had been using these medications for more than 30 days before study entry, they could continue with medication, but the dose and regimen could not be changed.

Patients could use contact lenses during the course of the study. Patients had to remove them before administration of the study drug and to wait for at least 15 minutes before reinserting them. On study visit days, these patients were instructed not to wear contact lenses.

Outcomes

The primary efficacy end point was the mean IOP (mm Hg) at each of the assessment time points (8 a.m., 10 a.m., and 4 p.m.) at each on-therapy study visit (week 2, week 6, and month 3). One eye from each patient was chosen as the study eye. Only the study eye was used in the efficacy analysis. If both eyes were treated, the worse evaluable eye was selected as the study eye. The worse eye was defined as the eye with the higher IOP at 8 a.m., averaged across the two eligibility visits.

IOP was measured using Goldmann applanation tonometry (GAT). The investigators took two consecutive IOP measurements in each eye. If the results differed by 4 mm Hg or less, the average was taken, while if the readings differed by more than 4 mm Hg, a third IOP reading was taken (the two closest IOP readings were then averaged).[2] The validity of GAT is discussed in Appendix 4. In general, GAT is expected to produce reliable IOP readings.

Supportive efficacy outcomes included:

- mean IOP change (mm Hg) from baseline and IOP percentage (%) change from baseline at each visit (week 2, week 6, and month 3) and assessment time point (8 a.m., 10 a.m. and 4 p.m.)
- the percentage of patients who achieved a target IOP level < 18 mm Hg at each visit and assessment time point

- the percentage of patients who achieved IOP-lowering of at least 30% from baseline at each visit and assessment time point.

Baseline IOP was determined by averaging the time-matched measurements from the two eligibility visits.

Safety was evaluated through a review of adverse events (AEs), assessments of BCVA, ocular signs (eyelids/conjunctiva, cornea, lens, and iris/anterior chamber including aqueous flare and inflammatory cells), visual field losses, ocular hyperemia, dilated fundus examinations, and central corneal thickness measurements. The schedule for safety population evaluation is described in Table 7.

Measurements of BCVA were performed at each visit using an Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at 3 m or 4 m. The baseline visual acuity was determined at the eligibility 2 visit. The change in BCVA was assessed from baseline to the three-month study visit.

Table 7: Schedule of the Safety Parameter Measurement

	Stage 1 (Screening / Eligibility)							Stage 2 (Treatment)								
	Screen	Eligibility 1			Eligibility 2			Week 2			Week 6			Month 3		
		8 a.m.	10 a.m.	4 p.m.	8 a.m.	10 a.m.	4 p.m.	8 a.m.	10 a.m.	4 p.m.	8 a.m.	10 a.m.	4 p.m.	8 a.m.	10 a.m.	4 p.m.
BCVA	X	X			X			X			X			X		
Ocular signs	X	X			X			X			X			X		
Visual field function	X													X		
CCT	X															X
Ocular hyperemia					X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundus	X															X

BCVA = best corrected visual acuity; CCT = central corneal thickness.

Source: Clinical study report.[2]

Statistical Analysis

Treatment-group differences in mean IOP were examined with a pairwise test for each on-therapy study visit and time point. Pairwise *t*-tests and confidence intervals (CIs) were based on the least squares means derived from a mixed-effects model for repeated measures.[20] The model accounted for correlated IOP measurements within-patient and included baseline IOP stratum and investigational centre as covariates.

Equivalence was concluded if the two-sided 95% CI for the difference in IOP (travoprost 0.003% PQ group minus travoprost 0.004% BAC group) was within 1.5 mm Hg at each of the three time points (8 a.m., 10 a.m., and 4 p.m.) for each on-therapy visit (week 2, week 6, and month 3). A second margin used in the equivalence testing was ± 1.0 mm Hg at the majority of time points (at least five of nine time points). These margins were recommended by the FDA clinical review team.[20]

Sample size estimate was based on an IOP standard deviation of 3.5 mm Hg, a 5% chance of a type I error and an assumption that the population means in the two groups were identical. A target enrolment of 720 patients was planned to ensure that at least 320 patients per treatment group were followed for three months, in order to provide

- ≥ 99% power that a 95% two-sided CI of the difference in IOP would fall within a 1.5 mm Hg margin, and
- ≥ 90% power that a 95% two-sided CI of the difference in IOP would fall within a 1.0 mm Hg margin.

No multiplicity adjustment was done, since results at all three time points across all on-therapy visits were required to satisfy the ± 1.5 mm Hg equivalence criteria.

Analysis Populations

The efficacy end points were evaluated based on the intention-to-treat (ITT) population, which included all patients who received study medication and had at least one scheduled on-therapy study visit. The per-protocol (PP) population was used for supportive analysis of the primary end point. The PP population included all those who received study medication

and had at least one scheduled on-therapy study visit. Safety was evaluated for patients who received at least one dose of study medication.

The primary and supportive efficacy analyses were based on observed cases, and missing data were not imputed.

Patient Disposition

The number of patient screened for eligibility has not been reported. A total of 864 patients were randomized, with 442 patients assigned to the travoprost 0.003% PQ group and 422 patients to the travoprost 0.004% BAC group. In total, 2.3% of patients in the travoprost 0.003% PQ group, and 3.3% of patients in the control group withdrew from the study.

Table 8: Patient Disposition

	Study C-11-034	
	Travoprost 0.003% PQ	**Travoprost 0.004% BAC**
Screened, N	Not reported	Not reported
Randomized, N	442	422
Discontinued, N (%)	10 (2.3)	14 (3.3)
Adverse events, N (%)	3 (0.7)	4 (0.9)
Lost to follow-up, N (%)	2 (0.5)	1 (0.2)
Patient's decision, N (%)	3 (0.7)	3 (0.7)
Noncompliance, N (%)	1 (0.2)	0 (0)
Inadequate control of IOP, N (%)	1 (0.2)	5 (1.2)
Other, N (%)	0 (0)	1 (0.2)
ITT, N	442	418
PP, N	436	415
Safety, N	442	421

ITT = intention-to-treat; PP = per-protocol.

Source: Peace et al. 2015.[1]

Exposure to Study Treatments

The extent of exposure to study drug was calculated as the number of days on therapy. "Days on therapy" was defined as the last day of exposure minus the first day, plus one. If the last day was not known, exposure was calculated as the date of last contact minus the first day of exposure, plus one.

No formal measures of treatment compliance were performed. During the on-therapy visits, designated study personnel asked the patients about their dosage compliance and reminded them to continue administration once daily at 8 p.m.

Table 9: Number and Percentage of Patients Exposed to Study Drug (Safety Population)

	Study C-11-034	
	Travoprost 0.003% PQ (n = 442)	**Travoprost 0.004% BAC (n = 421)**
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Clinical study report.[2]

Critical Appraisal

Internal Validity

No sources of bias that would seriously alter the results of the Study C-11-034 were identified. Randomization, allocation concealment, and blinding were done appropriately. Patients were randomly assigned to study groups using the interactive Web response system, the study was double-masked, and the external packaging of the study products was identical. As both treatment groups received the same drug, AEs from prostaglandin analogues (change in iris pigmentation or lengthening eyelashes) would occur in both

groups and were therefore unlikely to unblind patients to treatment assignment. In addition, the number of study withdrawals was low and balanced in both study arms, and the statistical model chosen provided robust analysis, given that the data missing were at random.

Adherence to treatment can affect the outcome, and no formal measurements of treatment compliance were performed during the study. However, there were no reported signs of overt lack of adherence that could be indicated through the number of empty bottles returned, the rate of AEs, or the mean differences in IOP between the groups.

GAT was used to measure IOP in the present study. The validity of GAT is discussed in detail in Appendix 4. In general, GAT is considered the gold standard in measuring IOP and is recommended for IOP measurement by the Canadian Ophthalmological Society glaucoma guidelines and the UK National Institute for Health and Care Excellence glaucoma guidelines.[3,21-23] GAT generally produces reliable IOP readings. However, there can be variability in IOP readings (around 1 mm Hg to 2 mm Hg, based on available evidence), depending on the observer and the timing of the measurements. The present study attempted to address variability by repeating IOP measurements (up to three times) and reporting an average reading.

Equivalency was shown at all three time points (8 a.m., 10 a.m., and 4 p.m.) at every follow-up visit (week 2, week 6, and month 3), for a total of nine successful equivalency tests for the pre-specified ± 1.5 mm Hg margin. In addition, the data were further assessed using a ± 1.0 mm Hg margin. There was no report on how the ± 1.5 margin was derived and how much it maintains efficacy of the reference over placebo. However, the clinical expert was satisfied with the margin that was suggested by the regulators, informing us that the margin also sits within the error margin of many methods of measuring IOP. The margin also appears to be an accurate representation of equivalence, as it is within the 1 mm Hg to 2 mm Hg variability of readings observed in the literature, depending on observer and time of day (Appendix 4). No multiplicity adjustment was done. This is acceptable, since all three time points (8 a.m., 10 a.m., and 4 a.m.) across all on-therapy visits had to satisfy the ± 1.5 mm Hg equivalence criteria.

Main proof of equivalence has been performed on the ITT analysis set. ITT analysis has generally been considered not conservative for equivalence trials, and the PP set would have been preferred for the analysis.[24] The ITT analysis set also includes the subjects who withdrew or dropped out from the study. Those who withdraw or drop out may have a lack of response to study drugs. For that reason, using the ITT analysis set may cause bias toward demonstrating equivalence. In Study C-11-034, the results for the primary end point have also been reported for the PP population, and the results were similar between the ITT and PP data sets. The results for the supportive efficacy outcomes have been reported only for the ITT analysis set. However, it should be noted that the numbers of patients in the ITT analysis set (n = 860) and PP analysis set (n = 851) are comparable.

External Validity

The clinical expert indicated that the choices of end points, duration of the study, and eligibility criteria are acceptable and clinically relevant. In addition, the baseline characteristics of the enrolled patients are representative of the population that would be treated with travoprost in Canada. However, the clinical expert acknowledged that more black patients were enrolled in the study than are generally seen in Canadian practice. Patients with higher elevations in IOP and more severe disease were excluded from the

trial, and therefore the applicability of the results to those with more severe disease is uncertain. The equivalence of the two formulations of travoprost is also uncertain in the context of comorbidities or combination therapy. Since no data on the pre-study IOP-lowering medications are presented, it is unclear whether the study results are applicable to treatment-naive patients.

According to the clinical expert, the treatment and follow-up period of three months is adequate to demonstrate IOP-lowering efficacy of glaucoma medications. The clinical expert also stated three months would likely be sufficient to see vision changes. As well, the washout periods for the pre-study IOP-lowering medications were adequate.

The comparator (travoprost 0.004% BAC) used in this trial does not correspond to available products on the Canadian market (travoprost 0.004% Z preserved with sofZia). Travoprost 0.004% BAC formulation is no longer marketed in Canada.[16] BAC has been associated with tolerability issues, and it seems to increase the incidence of hyperemia.[19] For that reason, the applicability of the safety results to Canadian practice are limited. However, the travoprost 0.003% PQ solution is identical to the formulation of travoprost 0.004% PQ marketed in Europe, with the exception of a lower concentration of the active substance. The EMA has concluded that no unexpected safety issues were identified when comparing travoprost 0.003% PQ with historical AEs data for travoprost 0.004% (preserved with BAC, sofZia or PQ).[19]

The manufacturer has justified the selection of travoprost 0.004% BAC solution as the comparator in the Study C-11-034 on the following basis: BAC-preserved formulation was used as a reference product in the clinical studies conducted to support the development of travoprost solutions preserved with sofZia or PQ; the safety and efficacy profiles of the BAC-preserved formulation are well established through clinical studies and more than 10 years of post-marketing experience; and travoprost 0.004% preserved with BAC was the only formulation approved in both the US and Europe, thus allowing a single clinical study to be conducted globally.

Drug therapy of OAG is characterized by poor compliance. However, no formal measures of treatment compliance were performed in the study.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 10, Table 11). However, not all efficacy outcomes identified in the protocol were reported in Study C-11-034. No data were available for mobility, quality of life, topical medication use, or compliance/adherence.

On-Therapy Intraocular Pressure

The on-therapy IOP values in the ITT population were similar between the travoprost 0.003% PQ and travoprost 0.004% BAC groups (Table 10) during all on-therapy study visits (weeks 2, week 6, and month 3) and assessment time points (8 a.m., 10 a.m., and 4 p.m. on each visit day). In patients taking travoprost 0.003% PQ, the average eye pressure (measured at 8 a.m.) was 19.4 mm Hg, 19.3 mm Hg, and 19.2 mm Hg, following two weeks, six weeks, and three months on treatment, respectively. The results were similar in patients taking travoprost 0.004% BAC (19.5 mm Hg, 19.3 mm Hg, and 19.3 mm Hg, respectively). The results were also similar at all study visits and assessment time points between the ITT and PP data sets.

Table 10: Key Efficacy Outcome

	Study C-11-034				
IOP (Intention-to-Treat Data)	**Travoprost 0.003% PQ**		**Travoprost 0.004% BAC**		**Mean Difference[a] (95% CI)**
	n (%)	(mm Hg)	n (%)	(mm Hg)	
Baseline, mean (SD)					
8 a.m.	442 (100)	26.9 (2.5)	418 (100)	27.1 (2.9)	NR
10 a.m.	442 (100)	25.4 (2.8)	418 (100)	25.6 (3.2)	NR
4 p.m.	442 (100)	24.6 (2.9)	418 (100)	24.8 (3.2)	NR
Week 2, mean ± SE					
8 a.m.	442 (100)	19.4 ± 0.16	416 (98.6)	19.5 ± 0.17	–0.1 (–0.5 to 0.3)
10 a.m.	442 (100)	18.6 ± 0.16	416 (98.6)	18.6 ± 0.16	0.0 (–0.4 to 0.4)
4 p.m.	442 (100)	18.0 ± 0.16	416 (98.6)	18.3 ± 0.16	–0.3 (–0.7 to 0.1)
Week 6, mean ± SE					
8 a.m.	439 (99.3)	19.3 ± 0.16	413 (97.9)	19.3 ± 0.17	0.0 (–0.4 to 0.4)
10 a.m.	440 (99.5)	18.5 ± 0.16	413 (97.9)	18.6 ± 0.17	–0.1 (–0.5 to 0.3)
4 p.m.	440 (99.5)	18.0 ± 0.16	413 (97.9)	18.1 ± 0.17	–0.2 (–0.6 to 0.2)
Month 3, mean ± SE					
8 a.m.	432 (97.7)	19.2 ± 0.17	408 (96.7)	19.3 ± 0.18	–0.1 (–0.5 to 0.3)
10 a.m.	432 (97.7)	18.3 ± 0.17	408 (96.7)	18.6 ± 0.18	–0.3 (–0.7 to 0.1)
4 p.m.	431 (97.5)	18.0 ± 0.16	408 (96.7)	18.0 ± 0.17	0.0 (–0.4 to 0.4)
IOP (Per-Protocol Data)	**Travoprost 0.003% PQ**		**Travoprost 0.004% BAC**		**Mean Difference[a] (95% CI)**
	n (%)	(mm Hg)	n (%)	(mm Hg)	
Baseline, mean (SD)					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2, mean ± SE					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6, mean ± SE					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 3, mean ± SE					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual Acuity (Safety Data)	**Travoprost 0.003% PQ**		**Travoprost 0.004% BAC**		
	n (%)	Number of letters read	n (%)	Number of letters read	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with Visual Acuity Change from Baseline to Month 3	**Travoprost 0.003% PQ (n = 438)**		**Travoprost 0.004% BAC (n = 418)**		

	Study C-11-034		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

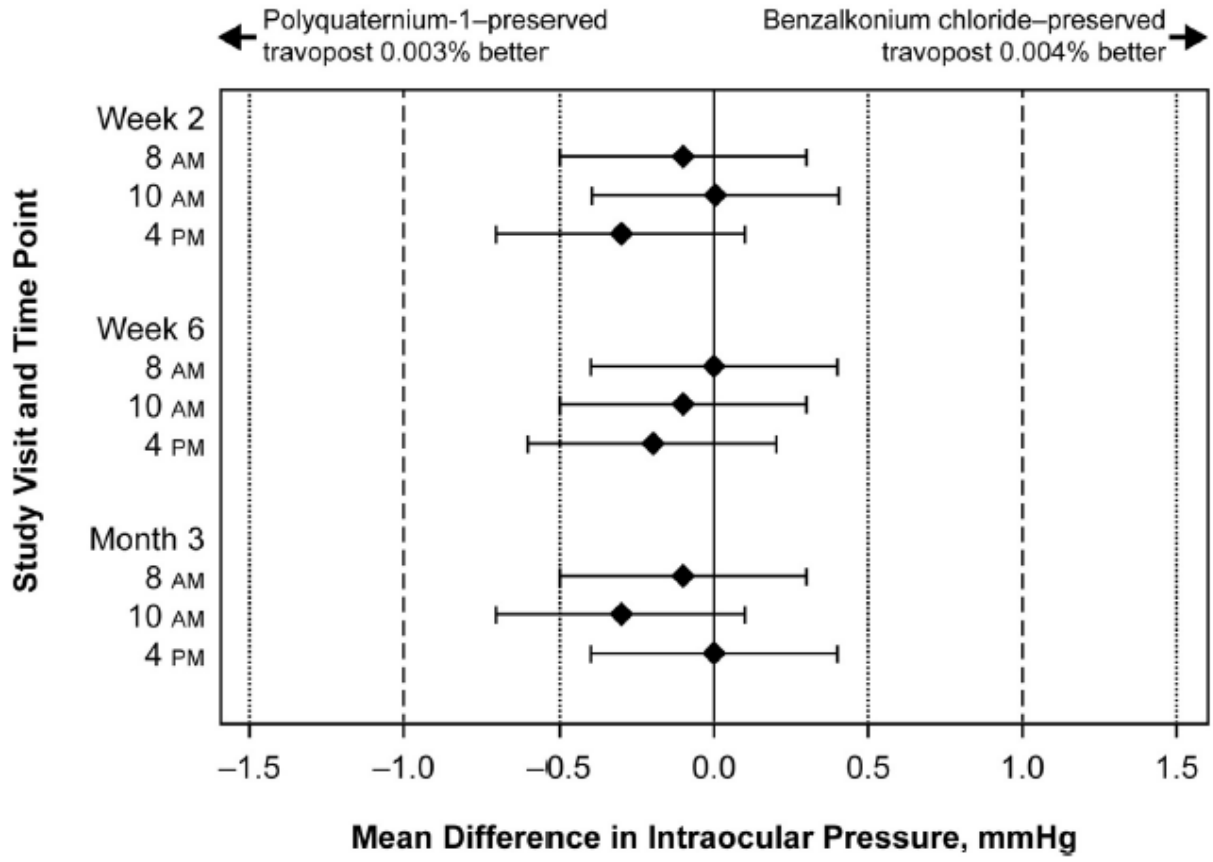
BAC = benzalkonium chloride; CI = confidence interval; IOP = intraocular pressure; NR = not reported; PQ = polyquaternium-1; SD = standard deviation; SE = standard error.

[a] Mean difference in observed IOP between treatment groups at each time point.

Source: Clinical study report.[2]

The least squares mean treatment-group differences ranged from –0.3 mm Hg to 0.0 mm Hg, with CIs ranging from –0.7 mm Hg to 0.4 mm Hg (Table 10 and Figure 2). Equivalence was met, since all nine of the assessments had CIs that were entirely within the pre-specified ± 1.5 mm Hg margin. Further, all nine of the assessments had CIs that were entirely within a ± 1.0 mm Hg margin.

Figure 2: Forest Plot Showing Mean Treatment Differences in Intraocular Pressure



CI = confidence interval.

Note: Data are presented as least squares mean (diamonds) and 95% CI (error bars).

Source: CADTH Common Drug Review submission.[17]

Visual Field Loss

The differences from baseline in BCVA were assessed as a safety variable in Study C-11-034. The results are reported in Table 10. In the travoprost 0.003% PQ group, [redacted] of patients had an increase, [redacted] had no change and [redacted] had a decrease in their visual acuity score. In the travoprost 0.004% BAC group, the respective proportions were [redacted], [redacted] and [redacted].

Function

No outcome relevant to function was reported in the study.

Quality of Life

No outcome relevant to quality of life was reported in the study.

Other Efficacy Outcomes

The mean change (measured in mm Hg) and percentage reduction in IOP from baseline to each study visit and assessment time point were similar between the treatment groups (Table 11). The mean reductions in IOP ranged from 7.6 mm Hg to 8.7 mm Hg in the travoprost 0.003% PQ group and from 7.5 mm Hg to 8.9 mm Hg in the travoprost 0.004% BAC group. The percentage reductions in IOP from baseline to each study visit and assessment time point ranged from 28.4% to 30.7% in the travoprost 0.003% PQ group and from 28.5% to 31.0% in the travoprost 0.004% BAC group. As well, the proportion of patients with an IOP measurement below 18 mm Hg or an IOP reduction of at least 30% relative to baseline was similar between the treatment groups throughout the study.

Table 11: Other Efficacy Outcomes[a] (Intention-to-Treat Data)

Study C-11-034					
Change (mm Hg) from baseline in IOP[b]	**Travoprost 0.003% PQ**		**Travoprost 0.004% BAC**		
	n (%)	Mean ± SE (mm Hg)	n (%)	Mean ± SE (mm Hg)	Mean difference[c] (95% CI)
Week 2					
8 a.m.	442 (100)	-8.5 ± 0.16	416 (98.6)	–8.6 ± 0.17	0.1 (–0.3 to 0.5)
10 a.m.	442 (100)	–7.7 ± 0.16	416 (98.6)	–8.0 ± 0.17	0.3 (–0.1 to 0.7)
4 p.m.	442 (100)	–7.6 ± 0.16	416 (98.6)	–7.5 ± 0.17	–01 (0.5 to 0.3)
Week 6					
8 a.m.	439 (99.3)	–8.6 ± 0.16	413 (97.9)	–8.8 ± 0.17	0.2 (–0.2 to 0.6)
10 a.m.	440 (99.5)	–7.8 ± 0.16	413 (97.9)	–8.0 ± 0.17	0.2 (–0.2 to 0.6)
4 p.m.	440 (99.5)	–7.6 ± 0.16	413 (97.9)	–7.7 ± 0.17	0.1 (–0.3 to 0.5)
Month 3					
8 a.m.	432 (97.7)	–8.7 ± 0.16	408 (96.7)	–8.9 ± 0.17	0.1 (–0.3 to 0.5)
10 a.m.	432 (97.7)	–8.0 ± 0.16	408 (96.7)	–8.0 ± 0.17	–0.0 (–0.4 to 0.4)
4 p.m.	431 (97.5)	–7.6 ± 0.16	408 (96.7)	–7.8 ± 0.17	0.2 (–0.2 to 0.6)
change (%) from baseline in IOP[d]	**Travoprost 0.003% PQ**		**Travoprost 0.004% BAC**		
	n (%)	% (SD)	n (%)	% (SD)	
Week 2					
8 a.m.	442 (100)	–29.7 (10.7)	416 (98.6)	–29.9 (11.3)	NR
10 a.m.	442 (100)	–28.4 (11.0)	416 (98.6)	–29.3 (11.4)	NR
4 p.m.	442 (100)	–28.7 (11.4)	416 (98.6)	–28.5 (11.6)	NR
Week 6					
8 a.m.	439 (99.3)	–30.3 (10.8)	413 (97.9)	–30.8 (11.4)	NR
10 a.m.	440 (99.5)	–28.9 (10.9)	413 (97.9)	–29.4 (11.4)	NR
4 p.m.	440 (99.5)	–28.8 (11.4)	413 (97.9)	–29.1 (11.1)	NR
Month 3					
8 a.m.	432 (97.7)	–30.7 (11.3)	408 (96.7)	–31.0 (10.9)	NR
10 a.m.	432 (97.7)	–29.5 (11.4)	408 (96.7)	–29.5 (11.5)	NR
4 p.m.	431 (97.5)	–28.5 (11.5)	408 (96.7)	–29.4 (11.4)	NR
Week 2					
Percentage of patients with IOP < 18 mm Hg[d]	**Travoprost 0.003% PQ**		**Travoprost 0.004% BAC**		
	n (%)	%	n (%)	%	
Week 2					
8 a.m.	442 (100)	33.3	416 (98.6)	36.8	NR

Study C-11-034					
10 a.m.	442 (100)	47.1	416 (98.6)	45.0	NR
4 p.m.	442 (100)	53.6	416 (98.6)	51.9	NR
Week 6					
8 a.m.	439 (99.3)	39.2	413 (97.9)	37.8	NR
10 a.m.	440 (99.5)	44.3	413 (97.9)	43.8	NR
4 p.m.	440 (99.5)	54.5	413 (97.9)	52.8	NR
Month 3					
8 a.m.	432 (97.7)	38.7	408 (96.7)	37.7	NR
10 a.m.	432 (97.7)	48.8	408 (96.7)	46.8	NR
4 p.m.	431 (97.5)	53.6	408 (96.7)	52.5	NR
Percentage of patients with ≥ 30% reduction in IOP[d]	**Travoprost 0.003% PQ**		**Travoprost 0.004% BAC**		
	n (%)	%	n (%)	%	
Week 2					
8 a.m.	442 (100)	49.5	416 (98.6)	47.4	NR
10 a.m.	442 (100)	43.9	416 (98.6)	48.3	NR
4 p.m.	442 (100)	47.1	416 (98.6)	44.2	NR
Week 6					
8 a.m.	439 (99.3)	52.8	413 (97.9)	52.3	NR
10 a.m.	440 (99.5)	45.5	413 (97.9)	49.9	NR
4 p.m.	440 (99.5)	44.5	413 (97.9)	47.5	NR
Month 3					
8 a.m.	432 (97.7)	53.7	408 (96.7)	54.4	NR
10 a.m.	432 (97.7)	52.8	408 (96.7)	50.0	NR
4 p.m.	431 (97.5)	44.5	408 (96.7)	48.3	NR

BAC = benzalkonium chloride; CI = confidence interval; IOP = intraocular pressure; NR = not reported; PQ = polyquaternium-1; SD = standard deviation; SE = standard error.

[a] No multiplicity adjustment was done; the results for other efficacy outcomes are hypothesis-generating only.

[b] Estimates from model that accounted for correlate IOP measurements within-patient, includes baseline IOP stratum and investigational centre as covariates.

[c] Mean difference between the treatment groups at each time point.

[d] Descriptive statistics used to summarize the estimates.

Source: Clinical study report.[2]

Harms

Only those harms identified in the review protocol are reported below.

Adverse Events

The safety profiles of travoprost 0.003% PQ and travoprost 0.004% BAC were similar (Table 12). The most common AE reported during the study was hyperemia of the eye (ocular or conjunctival). A numerically lower incidence of hyperemia was observed in travoprost 0.003% PQ group than in travoprost 0.004% BAC group (ocular hyperemia: 7.0% versus 8.1% and conjunctival hyperemia: 5.7% versus 7.1%, respectively), but absolute differences were small.

Serious Adverse Events

No serious AEs related to the study drug were reported in the study.

Withdrawals Due to Adverse Events

Three patients from the travoprost 0.003% PQ group and four patients from the travoprost 0.004% BAC group withdrew from the study due to AEs.

Mortality

No patient deaths were reported in the study.

Notable Harms

A numerically lower incidence of hyperemia was observed in the travoprost 0.003% PQ group than in the travoprost 0.004% BAC group (ocular hyperemia: 7.0% versus 8.1% and conjunctival hyperemia: 5.7% versus 7.1%, respectively). The incidence of other notable harms was less than 5%.

Table 12: Harms

	Study C-11-034	
AEs[a]	**Travoprost 0.003% PQ (N = 442)**	**Travoprost 0.004% BAC (N = 421)**
Subjects with > 0 AEs, N (%)	134 (30.3)	136 (32.3)
Most common AEs[b]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
SAEs		
Subjects with > 0 SAEs, N (%)	5 (1.1)	7 (1.7)
Treatment-related SAE	0	0
Non–treatment-related SAE	5 (1.1)	7 (1.7)
WDAEs		
WDAEs, N (%)	3 (0.7)	4 (1.0)
Treatment-related AE	2 (0.5)	3 (0.7)
Non–treatment-related AE	1 (0.2)	1 (0.2)
Deaths		
Number of deaths, N (%)	0	0
Notable Harms		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AE = adverse event; BAC = benzalkonium chloride; PQ = polyquaternium-1; SAE = serious adverse event; WDAE = withdrawals due to adverse events.

[a] Overall frequency of AEs (related and unrelated to treatment).

[b] Frequency > 1%.

Source: Clinical study report.[2]

Discussion

Summary of Available Evidence

The clinical review was based on one randomized multi-centre clinical trial (Study C-11-034), in which patients were randomized to travoprost 0.003% PQ (n = 442) or travoprost 0.004% BAC (n = 422) once daily for three months. The primary objective of this study was to demonstrate that the IOP-lowering efficacy of travoprost 0.003% PQ is equivalent to that of travoprost 0.004% BAC in patients with OAG or ocular hypertension. The primary efficacy end point was the mean IOP (measured in mm Hg) assessed at 8 a.m., 10 a.m., and 4 p.m. at week 2, week 6, and month 3 on-therapy study visits. Equivalence was concluded if the two-sided 95% CI for the difference in IOP (travoprost 0.003% group minus travoprost 0.004% group) was within 1.5 mm Hg at each of the three time points (8 a.m., 10 a.m., and 4 p.m.) for each on-therapy visit (week 2, week 6, and month 3). The manufacturer did not provide justification for using this margin (i.e., it did not conduct meta-analyses of travoprost 0.004% effect over placebo and determine a minimum percentage of maintaining efficacy). However, this margin was recommended by the FDA clinical review team, and the clinical expert consulted on this review found it clinically acceptable.

The choice of the main outcome is standard among trials of ocular hypertension and glaucoma. The change in IOP has been associated with reduction in optic nerve damage and in loss of visual function. The use of GAT is considered the standard in measuring IOP (Appendix 5). Further generalization beyond the existing evidence between travoprost 0.003% PQ and travoprost 0.004% BAC is limited, as we are unable to ascertain a minimal clinically important difference for the reduction in IOP; the Canadian Ophthalmological Society guideline suggests treatment should aim at a certain IOP upper limit, based on the stages of optical nerve damage. Hence, the clinical benefit for each patient is different and is based on the severity of nerve damage.

The key limitation of Study C-11-034 is that equivalence was determined versus BAC-preserved travoprost 0.004% instead of the sofZia-preserved travoprost 0.004% formulation available in Canada. Travoprost 0.004% BAC formulation is no longer marketed in Canada.[16] BAC has been associated with tolerability issues, and it seems to increase the incidence of hyperemia.[19] For that reason, the applicability of the safety results to Canadian practice is limited. However, the travoprost 0.003% PQ solution is identical to the formulation of travoprost 0.004% PQ marketed in Europe, with the exception of a lower concentration of the active substance. The EMA has concluded that no unexpected safety issues were identified when comparing travoprost 0.003% PQ and historical AEs data for travoprost 0.004% (preserved with BAC, sofZia, or PQ).[19] Other major limitations affecting the internal or external validity of the study were not identified.

The manufacturer has justified the selection of travoprost 0.004% BAC solution as the comparator in Study C-11-034 on the following basis: BAC-preserved formulation was used as a reference product in the clinical studies conducted to support the development of travoprost solutions preserved with sofZia or PQ; the safety and efficacy profiles of the BAC-preserved formulation are well established through clinical studies and more than 10 years of post-marketing experience; and travoprost 0.004% preserved with BAC was the only formulation approved in both the US and Europe, thus allowing a single clinical study to be conducted globally.

Interpretation of Results

Efficacy

Results from this study show that the IOP-lowering efficacy of travoprost 0.003% PQ is equivalent to that of travoprost 0.004% BAC formulation. Equivalence was shown, as the two-sided 95% CI for the difference in IOP between treatment groups was within the pre-specified ± 1.5 mm Hg margin at each of the three assessment time points (8 a.m., 10 a.m., and 4 p.m.) for each on-therapy visit (week 2, week 6, and month 3). Further, all nine of the assessments had 95% CIs that were entirely within a ± 1.0 mm Hg margin. Mean IOP reductions from baseline ranged from 7.6 mm Hg to 8.7 mm Hg for travoprost 0.003% PQ and from 7.5 mm Hg to 8.9 mm Hg for travoprost 0.004% BAC, corresponding to IOP reductions of 28.7% to 30.7%, and 28.5% to 31.0%, respectively.

No sources of bias that would seriously alter the efficacy results of Study C-11-034 were identified. In addition, no major factors that would affect the external validity (applicability or generalizability) of the efficacy results to Canadian practice were identified. The use of BAC-preserved travoprost 0.004% instead of the sofZia-preserved travoprost 0.004% as a comparator in the study is not expected to affect the IOP-lowering efficacy of travoprost.

No long-term data on the effects of travoprost 0.003% PQ formulation were identified. However, the long-term studies (up to five years) of travoprost 0.004% BAC have demonstrated the maintenance of the effect without development of tolerance.[19]

No network meta-analyses on the effects of travoprost 0.003% PQ compared with its treatment alternatives were identified.

Harms

The safety profiles of travoprost 0.003% PQ and travoprost 0.004% BAC were similar. A numerically lower incidence of hyperemia of the eye was, however, observed in patients exposed to travoprost 0.003% PQ compared with those administered travoprost 0.004% BAC.

Both the concentration of the active substance and the preservative used in the formulation can modify the safety profile of travoprost product. For example, higher incidence of hyperemia has been associated with travoprost formulations preserved with BAC than with travoprost solutions preserved with sofZia or PQ.[19] Since the comparator (travoprost 0.004% BAC) used in this study does not correspond to the available products on the Canadian market (travoprost 0.004% Z), the applicability (external validity) of safety results is limited.

The EMA has compared the safety data from Study C-11-034 with clinical trials involved in the development of travoprost 0.004% BAC (C-97-79, C-97-72 and C-97-71), travoprost 0.004% Z (C-04-17), and travoprost 0.004% PQ (C-08-40).[19] The EMA has concluded that the adverse events reported for both treatment groups during Study C-11-034 were generally consistent with the known safety profile of travoprost.

Potential Place in Therapy[1]

Prostaglandin analogues, including travoprost, are the currently first-line therapy for glaucoma. Travoprost 0.004% preserved with sofZia is widely used as initial therapy. Travoprost 0.004% generic versions in Canada currently also use sofZia as a preservative.

The proposed advantage of travoprost 0.003% PQ is a reduced rate of adverse effects, namely, reduced hyperemia. However, based on the evidence in this review, the rate of hyperemia is only slightly numerically lower with travoprost 0.003% PQ than travoprost 0.004% BAC, and no statistical comparison was made for this outcome. No comparison was available for the most relevant comparator, travoprost 0.004% preserved with sofZia.

Travoprost 0.003% PQ will provide an alternative for the niche of patients who are intolerant to drops containing BAC and/or sofZia, and having access to prostaglandin analogues without BAC is important for these patients. However, current alternative formulations of travoprost available in Canada do not contain BAC and can be used to manage patients with intolerance to BAC.

As comparisons with travoprost 0.004% Z are not available to evaluate comparative IOP-lowering effect or safety, there is little to no evidence that travoprost 0.003% PQ provides significant advantages over currently available formulations of travoprost in Canada.

[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

Travoprost 0.003% PQ appears similarly efficacious and safe compared with travoprost 0.004% BAC, although data on patient-reported outcomes are not available from the trial included in this review. In addition, evidence on the comparative efficacy and safety of travoprost 0.003% PQ versus other IOP-lowering therapies is lacking.

In Study C-11-034, travoprost 0.003% PQ provided IOP-lowering efficacy equivalent to that of travoprost 0.004% BAC in the treatment of patients with ocular hypertension or OAG. The AEs reported in the study were local ocular effects consistent with the known safety profile of travoprost. The most common AE reported was hyperemia of the eye (ocular or conjunctival). However, the comparator used in this trial had a different preservative than that currently available in the Canadian market (travoprost 0.004% preserved with sofZia). Because formulations preserved with BAC have been associated with higher incidence of hyperemia than formulations preserved with sofZia or PQ, we are not certain whether the safety profile seen with travoprost 0.003% PQ would be similar to the travoprost 0.004% Z used in Canada. However, the travoprost 0.003% PQ solution is identical to the formulation of travoprost 0.004% PQ marketed in Europe, with the exception of a lower concentration of the active substance, travoprost. The EMA has concluded that no unexpected safety issues were identified when comparing travoprost 0.003% PQ solution and historical AEs data for travoprost 0.004% (preserved with BAC, sofZia or PQ).

Appendix 1: Patient Input Summary

No patient input was provided by patient groups.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations MEDLINE Epub Ahead of Print **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 28, 2017
Alerts:	Bi-weekly search updates until July 19, 2017 (date of CDEC meeting)
Study Types:	Randomized controlled trials; controlled clinical trials
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
MeSH	Medical 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
exp	Explode a subject heading
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)
.pt	Publication type
.rn	Registry number (CAS, UNII)
.nm	Name of substance word
.tn	Drug trade name (Embase)
ppez	Ovid database code; MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

Multi-database Strategy	
Line #	Searches
1	(Travoprost* or Izba* or Travatan or AL-6221 or AL6221 or fluprostenol isopropyl ester* or Avatan or Avost or Avro or Hlavtan or Trapost or Travatanz or Travotan).ti,ab,kf,ot,hw,rn,nm.
2	(WJ68R08KX9 or 157283-68-6 or 207742-69-6).rn,nm.
3	or/1-2
4	3 use ppez

Multi-database Strategy	
5	Izba.tn.
6	*travoprost/
7	(Travoprost* or Izba* or Travatan or AL-6221 or AL6221 or fluprostenol isopropyl ester or Avatan or Avost or Avro or Hlavtan or Trapost or Travatanz or Travotan).ti,ab,kw.
8	or/5-7
9	8 not conference abstract.pt.
10	9 use oemezd
11	4 or 10
12	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
13	Randomized Controlled Trial/
14	exp Randomized Controlled Trials as Topic/
15	"Randomized Controlled Trial (topic)"/
16	Controlled Clinical Trial/
17	exp Controlled Clinical Trials as Topic/
18	"Controlled Clinical Trial (topic)"/
19	Randomization/
20	Random Allocation/
21	Double-Blind Method/
22	Double Blind Procedure/
23	Double-Blind Studies/
24	Single-Blind Method/
25	Single Blind Procedure/
26	Single-Blind Studies/
27	Placebos/
28	Placebo/
29	Control Groups/
30	Control Group/
31	(random* or sham or placebo*).ti,ab,hw,kf,kw.
32	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
33	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
34	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
35	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
36	allocated.ti,ab,hw.
37	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
38	or/12-37
39	11 and 38
40	exp animals/
41	exp animal experimentation/ or exp animal experiment/
42	exp models animal/
43	nonhuman/
44	exp vertebrate/ or exp vertebrates/
45	or/40-44
46	exp humans/
47	exp human experimentation/ or exp human experiment/
48	or/46-47
49	45 not 48
50	39 not 49
51	remove duplicates from 50

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

Grey Literature

Dates for Search:	March 2017
Keywords:	Izba, travoprost, glaucoma, ocular hypertension
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/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

No studies were excluded.

Appendix 4: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

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

Findings

Goldmann Applanation Tonometry

GAT is considered the gold standard in measuring IOP and is recommended for IOP measurement by the Canadian Opthalmological Society glaucoma guidelines and the UK National Institute for Health and Care Excellence glaucoma guidelines.[3,21-23] To measure IOP for the study described in the present submission, the investigators took two consecutive IOP measurements in each eye.[2] If the results differed by 4 mm Hg or less, the average was taken, while if the readings differed by more than 4 mm Hg, a third IOP reading was taken (the two closest IOP readings were then averaged).

The reliability of IOP measurement using GAT has been evaluated in two studies. Dielemans et al. assessed the reliability of GAT in 62 patients (mean age 69.6 years) with and without glaucoma.[22] They measured inter-observer and intra-observer variation in IOP measurements in both eyes. For the inter-observer study, two different observers measured IOP three times consecutively 10 minutes apart. For the intra-observer study, the same observer measured IOP three times consecutively 10 minutes apart. The investigators measured the median IOP, standard deviation (SD), and coefficient of variation for each set of three measurements. For the inter-observer study, they measured the mean difference in median IOP measurement between observers (i.e., difference in median of three IOP measurements). The correlation between median IOP reading was also calculated for two observers. For the intra-observer study, the mean difference in median values of IOP was compared for each set of three measurements within observers. For both the intra-observer and inter-observer studies, the authors compared the mean difference of first IOP readings from each set of three. The authors reported that the mean difference in median IOP measurements was 1.60 mm Hg (SD 2.15 mm Hg) between observers for the inter-observer study. The correlation coefficient between observers was 0.75 for the right eye and 0.87 for the left eye. For the intra-observer study, the mean difference in median IOP within observers was 1.50 mm Hg (SD 1.96 mm Hg). The authors also reported that the mean difference between first IOP readings from each set of three was 1.79 mm Hg (SD 2.41 mm Hg) between observers (inter-observer) and 1.64 mm Hg (SD 2.07 mm Hg) within observers (intra-observer). The authors compared the first IOP reading of each set with the median value from the set and 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. However, the clinical relevance of this decrease in variability is uncertain.

A study by Sudesh et al. examined accuracy and variability in IOP measurement using GAT.[21] This study evaluated inter-observer and intra-observer variability among eight tonometrists examining 16 patients. The tonometrists were randomly assigned to receive a review of training on GAT or no training. Four consecutive IOP readings were taken by one

observer on one eye, followed by four consecutive readings from another observer on the same eye. The second observer then took four IOP readings for the other eye, followed by four readings from the first observer. The authors reported the mean IOP reading in trained versus untrained tonometrists and presented the mean IOP readings from each tonometrist. The difference in mean IOP reading in trained versus untrained tonometrists was 1.12 mm Hg (standard error [SE] 0.44 mm Hg). The largest difference between any two tonometrists was 1.84 mm Hg (no measure of precision provided). 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 less for 26% of observers and 3 mm Hg or less for 19% of observers.

The results of these two studies suggest that GAT generally produces reliable IOP readings. However, there can be variability (around 1 mm Hg to 2 mm Hg based on available evidence) in IOP readings, depending on the observer and timing of the measurements. The present submission attempted to address variability by repeating IOP measurements (up to three times) and reporting an average reading. This is similar to the approach of Dielemans et al., as the first IOP reading of a set may be slightly higher than the median of three readings.

Intraocular Pressure

As the IOP is measured through other instruments, validity and reliability depend on the tool used to measure the IOP. We aimed to search the literature for a published minimal clinically important difference or assessment of the correlation between IOP and clinical prognosis. However, no minimal clinically important difference was found in the literature.

Correlation of IOP Lowering With Clinical Outcomes

A 2013 US Preventive Services Task Force systematic review evaluated the effect of medical treatment (topical medications) on optic nerve damage and visual field loss.[25] The authors located three systematic reviews and 21 randomized controlled trials (RCTs) that addressed this outcome. They reported that there was high-quality evidence that lowering IOP reduces risk of optic nerve damage and visual field loss. However, there was insufficient evidence on the effect of glaucoma treatment on patient-reported outcomes (quality of life, activity limitation, or patient-reported visual loss).

A 2005 systematic review and meta-analysis specifically evaluated the effect of treating ocular hypertension and open-angle glaucoma compared with no treatment.[26] The meta-analysis included five RCTs of patients with ocular hypertension and found 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). Two RCTs in patients with glaucoma were included in the meta-analysis; in these RCTs, treatment of glaucoma reduced rate of progression of visual field loss compared with no treatment (HR 0.65, 95% CI 0.49 to 0.87). There was no formal quality assessment performed in this systematic review.

Clinical Correlation With Lowering IOP by a Threshold of 30% or Greater

The investigators for this submission evaluated the proportion of patients achieving > 30% lowering of IOP over the study period. Canadian guidelines recommend a target IOP-lowering of > 30% in patients with moderate to severe glaucoma (and of > 25% in patients

with early disease).[3] This is based on evidence that lowering IOP by > 25% to 30% can slow progression of disease and reduce risk of vision loss.[27,28]

Only one identified trial specifically evaluated the effect of lowering IOP by 30% on glaucoma progression. In a 1998 RCT, 140 patients (mean age 66, with normal-tension glaucoma) were randomized to (1) treatment of one eye to lower IOP by 30% or (2) no treatment.[27] The authors compared the proportion of patients reaching the primary end point (visual field loss or optic disk progression), as well as the time to primary end point, in treated versus untreated eyes. Patients were followed a minimum of every three months for the first year of the study and every six months thereafter (median follow-up time not reported). Fewer patients in the treatment group reached the primary end point (12% treated versus 35% untreated). The mean time to the primary end point was 1,695 ± 143 days in the treated group compared with 2,688 ± 123 days in the untreated group. Patients could not be using beta blockers or adrenergic agonists; however, the specific medications used in the treated group were not reported. Further, this study included only patients with normal-tension glaucoma.

One RCT evaluated treatment versus no treatment in patients with early open-angle glaucoma and visual field defects.[28] This study randomized 255 patients (median age 68 years) to receive either laser trabeculoplasty plus topical betaxolol or no treatment. Visual field tests and tonometry were performed every three months, and optic disk photography was performed every six months. The primary outcome was glaucoma progression (measured by detecting visual field defects or optic disk cupping). In the treatment group, the IOP decreased by 25% from baseline compared with no change in the control group. The authors report that the reduction was more pronounced (29%) in patients with a baseline IOP of 21 mm Hg or more compared with those with an IOP less than 21 mm Hg at baseline (18%). The reduction in IOP for treated patients was maintained over the follow-up period (median duration of follow-up was six years). The primary end point occurred at a lower rate in treated patients compared with controls (45% versus 62%, $P = 0.007$). The authors concluded that lowering of IOP by 25% reduced the risk of progression of glaucoma. The intervention in this study involved laser trabeculoplasty and a topical beta blocker; therefore, the applicability of the results to those using topical prostaglandin analogues alone (i.e., travoprost) or any other treatment or combination of treatments is uncertain.

The results of these two trials suggest that lowering IOP by 25% to 30% reduces risk of progression of glaucoma. This would support the threshold used by the investigators for the present submission. It is important to note, however, that the interventions used in these RCTs did not match that used for the present submission (travoprost 0.003%). Therefore, whether lowering IOP by > 30% with travoprost 0.003% reduces risk of progression of glaucoma is uncertain.

Conclusion

GAT generally produces reliable IOP readings. However, there can be variability in IOP readings (around 1 mm Hg to 2 mm Hg based on available evidence), depending on the observer and timing of the measurements. The present submission attempted to address variability by repeating IOP measurements (up to three times) and reporting an average reading. This is similar to the approach of Dielemans et al., as the first IOP reading of a set may be slightly higher than the median of three readings. Five RCTs of patients with ocular hypertension found that reducing IOP decreased the rate of progression to glaucoma

compared with no treatment (HR 0.56, 95% CI 0.39 to 0.81). The results of two trials suggest that lowering IOP by 25% to 30% reduces risk of progression of glaucoma.[27,28] This supports the threshold used by the investigators for the present submission. It is important to note, however, that the interventions used in these RCTs did not match that used for the present submission (travoprost 0.003%). Therefore, whether lowering IOP by > 30% with travoprost 0.003% reduces risk of progression of glaucoma is unclear.

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