

Efficacy and tolerability of benzalkonium chloride-free travoprost in glaucoma patients switched from benzalkonium chloride-preserved latanoprost or bimatoprost

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Introduction: The preservative benzalkonium chloride (BAK) is used to preserve several topical, intraocular pressure (IOP)-lowering glaucoma medications but can cause tolerability concerns that may lead to decreased adherence to treatment and ultimately diminish the effectiveness of IOP control. The study aimed to determine the efficacy and tolerability of BAK-free travoprost preserved with polyquaternium-1 in glaucoma patients switched from BAK-preserved latanoprost or bimatoprost.

Methods: This 12-week, open-label study was conducted in Europe between December 2011 and February 2013. We enrolled adult patients with open-angle glaucoma or ocular hypertension who were receiving BAK-preserved latanoprost 0.005% or bimatoprost 0.01% and, in the opinion of the investigator, would benefit from transition to BAK-free travoprost 0.004% preserved with polyquaternium-1 because of tolerability concerns. Assessments included IOP, proportion of patients with IOP \leq 18 mmHg, ocular surface status, hyperemia, patient treatment preference, and adherence. Adverse events were recorded throughout the study.

Results: Of the 202 patients screened, 187 patients were included in the intent-to-treat population (mean age, 66.6 years; range, 19–90 years). The mean IOP significantly reduced from baseline (17.0 mmHg) to week 6 (mean change, -1.17 mmHg; $P < 0.001$) and week 12 (-1.16 mmHg; $P < 0.001$). At week 12, more patients achieved IOP \leq 18 mmHg (81.2% versus 73.3% at baseline), and ocular surface disease severity improved from baseline to week 12. Most patients preferred BAK-free travoprost (74.9%) versus their previous medication and were very confident in their adherence (84.1%). Reduced visual acuity and eye pruritus were the most common adverse events (2.5% each).

Conclusion: BAK-free travoprost 0.004% preserved with polyquaternium-1 was efficacious and well tolerated and may be an advantageous prostaglandin analog option for patients with open-angle glaucoma or ocular hypertension who are intolerant to BAK-preserved latanoprost or bimatoprost.

Keywords: benzalkonium chloride, intraocular pressure, polyquad, polyquaternium-1, prostaglandin analog, switch, travoprost

Introduction

Glaucoma is a progressive disease affecting the optic nerve¹ and is the second leading cause of blindness worldwide.² The etiology of glaucoma is multifactorial, but elevated intraocular pressure (IOP) has been associated with the risk and progression of the disease, resulting in visual field loss and optic disk cupping.^{1,3–5} Reduction of IOP is the

only evidence-based treatment strategy for slowing glaucoma progression.¹ To reduce IOP to target levels, the European Glaucoma Society and previous studies recommend a therapy with topical medications as initial treatment.⁶⁻⁸

Several topical, IOP-lowering medications are available, but prostaglandin analogs (eg, latanoprost, bimatoprost, tafluprost, and travoprost), which reduce IOP by increasing uveoscleral outflow of aqueous humor, are recommended as the first-line therapies by the European Glaucoma Society and previously reported studies because of their efficacy, favorable side-effect profile, and convenience.⁶⁻⁹ Latanoprost, bimatoprost, and travoprost provide greater IOP reduction than β -blockers; however, this increased efficacy is accompanied by a greater incidence of ocular hyperemia.¹⁰⁻¹³ A randomized, parallel-group, single-masked study (n=410) showed similar IOP-lowering efficacies of bimatoprost, latanoprost, and travoprost.¹⁴ Travoprost has been shown to maintain a mean IOP reduction of 30% throughout a 24-hour dosing interval¹⁵ and was more efficacious than latanoprost over a 48-hour period after the last dose.¹⁶ Among prostaglandin analogs, peak percentage reductions in IOP were similar with bimatoprost (33%), latanoprost (31%), and travoprost (29%),¹⁷ with higher rates of ocular hyperemia reported with travoprost 0.004% and bimatoprost 0.03% compared with latanoprost 0.005%.^{10,12,17}

Benzalkonium chloride (BAK) is the most commonly used preservative in ophthalmic medications and has been associated with various ocular surface symptoms, including hyperemia, burning, stinging, punctate keratitis, foreign body sensation, and dry eye.¹⁸⁻²⁰ Bimatoprost 0.01% and latanoprost 0.01% each contain 0.02% BAK, and travoprost 0.004% contains 0.015% BAK. These BAK concentrations have been shown to exert cytotoxic effects on cultured conjunctival and corneal epithelial cells and trabecular meshwork cell lines^{21,22} and cause pathologic alterations in corneal and conjunctival morphologies in animal models.²³

In an effort to reduce ocular symptoms and avoid the corneal damage and tear film disruption associated with chronic BAK exposure,²⁴ a BAK-free formulation of travoprost 0.004% containing the preservative polyquaternium-1 has been developed. In a randomized, multicenter, parallel-group, double-masked study, BAK-free travoprost preserved with polyquaternium-1 provided IOP control equivalent to that with BAK-preserved travoprost, with a lower incidence of ocular hyperemia.²⁵ Limited data are available regarding the comparisons of polyquaternium-1-preserved travoprost with BAK-preserved formulations of other prostaglandin analogs.

The present study aimed to assess the efficacy and tolerability of BAK-free travoprost 0.004% preserved with polyquaternium-1 in patients with open-angle glaucoma or ocular hypertension who were intolerant to BAK-preserved latanoprost 0.005% or bimatoprost 0.01%.

Methods

This 12-week, open-label, single-group study ([ClinicalTrials.gov](https://clinicaltrials.gov) ID, NCT01493427; EudraCT ID, 2011-003816-21) was performed in Belgium, Spain, Italy, and Sweden between December 2011 and February 2013. The study was approved by the ethical committees of the following institutions: Hospital Clinico San Carlos-IdISSC, Hospital Ramon y Cajal, and Policlínico San Mateo, and was compliant with the Health Insurance Portability and Accountability Act and the ethical standards set forth by the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before any screening procedures were performed.

Patients eligible for inclusion were aged ≥ 18 years with open-angle glaucoma or ocular hypertension who were receiving treatment with BAK-preserved latanoprost 0.005% or bimatoprost 0.01% (branded or generic) for ≥ 4 weeks and who, in the opinion of the investigator, would benefit from a therapeutic switch because of tolerability concerns (based at the discretion of the study investigators). IOP in both eyes must have been safe in the opinion of the investigator such that vision and optic nerve integrity were maintained. In addition, IOP must have been < 30 mmHg while receiving latanoprost or bimatoprost. If the nonstudy eye required a pharmacologic therapy for IOP control, it was required to be controlled with the study medication alone (ie, BAK-free travoprost 0.004%). A best-corrected visual acuity of at least 6/60 Snellen (1.0 logMAR) was required in both eyes. All patients had to be willing and able to provide informed consent and discontinue other ocular hypotensive medications.

Women who were pregnant or lactating were not allowed to participate. Patients with any abnormality that prevented reliable applanation tonometry; patients with corneal dystrophy, conjunctivitis, keratitis, uveitis, or progressive retinal or optic nerve disease; and patients who had an intraocular or laser surgery ≤ 3 months before screening were excluded. Use of punctal plugs, punctal cautery, cyclosporine ophthalmic emulsion (Restasis®; Allergan, Inc., Irvine, CA, USA), or topical ocular corticosteroids for dry eye or keratoconjunctivitis sicca was not allowed. Systemic medications capable of altering IOP were permitted but must have been stabilized for ≥ 7 days before screening.

Eligible patients discontinued latanoprost or bimatoprost and self-administered one drop of BAK-free travoprost 0.004% preserved with polyquaternium-1 (Travatan® preserved with POLYQUAD®; Alcon Laboratories, Inc., Fort Worth, TX, USA) every evening at ~8 pm for 12 weeks. No washout period was planned between medications. If only one of the patient's eyes was dosed, the dosed eye was selected for analysis. If both eyes were dosed, then the worse evaluable eye was selected for analysis. The worse eye was the eye with the higher IOP at the screening visit. If both eyes were equal, then the right eye was selected for analysis.

IOP was assessed using Goldmann applanation tonometry at the screening/baseline visit and during on-therapy visits at weeks 6 (± 3 days) and 12 (± 3 days), at approximately the same time of day (± 1 hour). To minimize confounding variables, all IOP measurements for individual patients were performed by the same operator using the same tonometer.

The primary efficacy endpoint was mean IOP change from baseline at week 12; IOP change from baseline to week 6 provided supportive data. The proportion of patients who achieved a target IOP of ≤ 18 mmHg at week 12 was a secondary endpoint; all other assessments were considered exploratory.

Adverse events (AEs) were recorded at each study visit and coded based on the Medical Dictionary for Regulatory Activities Version 15.0.

Descriptive statistics was provided for all study endpoints. The mean IOP change from baseline at week 12 was analyzed using a paired *t*-test. To assess the effect of time on IOP, the mean IOP at baseline, week 6, and week 12 was analyzed using a mixed model that included visit and current treatment (ie, latanoprost 0.005% and bimatoprost 0.01%) as fixed effects and the visit by treatment interaction and patients as random effects. Differences in the ocular symptom surveys from baseline to week 12 were analyzed using Wilcoxon signed-rank tests. Global preference responses were analyzed using an exact binomial test. Statistical analysis was performed using the SAS® 9.1.3 software (SAS Institute, Cary, NC, USA), with *P*-values < 0.05 considered statistically significant.

Results

Of the 202 patients screened, 201 patients were eligible for participation and 179 patients completed the study (Figure 1). Two patients withdrew consent and did not receive the study drug; thus, 199 patients received ≥ 1 dose of the study medication (safety population). Of these, 187 patients completed ≥ 1 on-therapy visit and were defined as the intent-to-treat (ITT) population. Patients who received study medication, completed all study visits, and satisfied inclusion

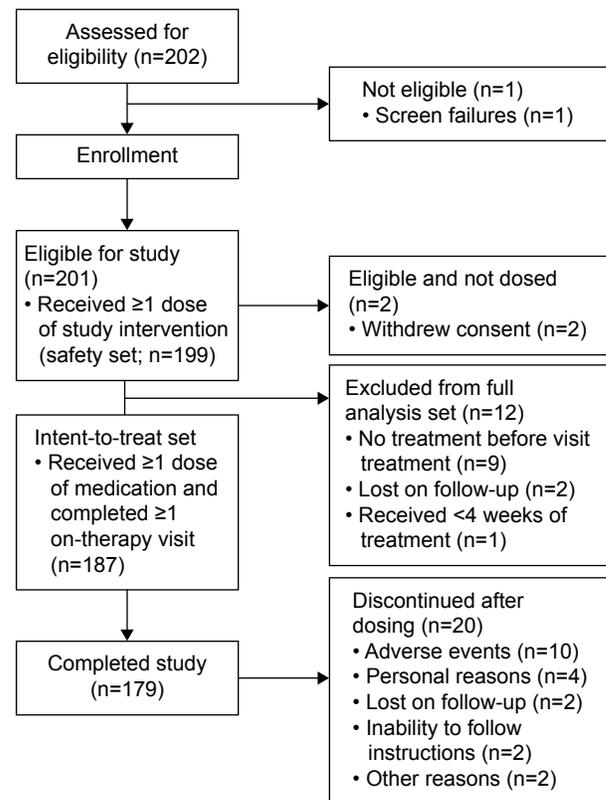


Figure 1 Patient flow chart.

and exclusion criteria were included in the per-protocol population ($n=144$).

The mean patient age was 66.6 years (range, 19–90 years; Table 1). Most patients were women (58.8%) and received latanoprost before transition to travoprost (78.4%).

Efficacy results were similar in the ITT and per-protocol data sets; results for the ITT population are reported. The mean IOP was significantly reduced by 5.85% from baseline to week 12 (-1.16 mmHg; $P < 0.001$; Figure 2); a similar IOP reduction was evident at week 6. Patients who had previously received latanoprost or bimatoprost at baseline had similar reductions in IOP at both time

Table 1 Patient baseline characteristics

Demographic	BAK-free travoprost (n=199)
Mean age (\pm SD) (years)	66.6 (11.7)
Sex, n (%)	
Female	117 (58.8)
Male	82 (41.2)
Treatment at baseline, n (%)	
Latanoprost	156 (78.4)
Bimatoprost	43 (21.6)

Abbreviations: BAK, benzalkonium chloride; SD, standard deviation.

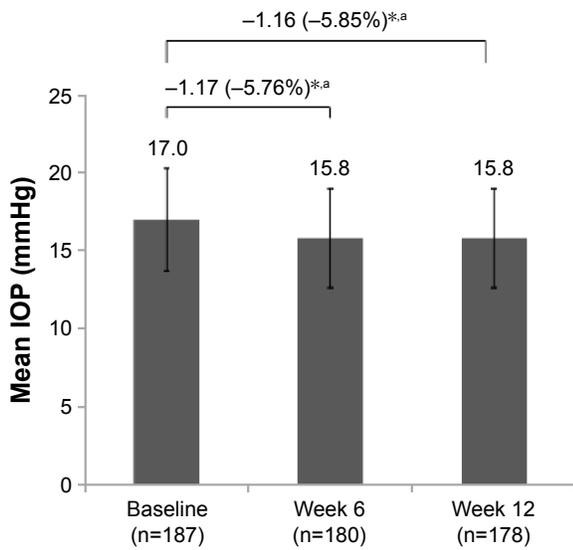


Figure 2 Mean (\pm SD) IOP throughout the study and change from baseline. **Notes:** * $P < 0.001$; mixed-model analysis. ^aData are presented as the difference of the mean (%). **Abbreviations:** IOP, intraocular pressure; SD, standard deviation.

points (latanoprost: -1.24 mmHg to -1.50 mmHg; bimatoprost: -1.05 mmHg to -1.16 mmHg; $P \leq 0.004$ versus baseline for all time points and previous treatment groups). The proportion of patients who achieved an IOP of ≤ 18 mmHg

was greater at week 6 (80.0%; $n=144/180$) and week 12 (81.2%; $n=147/181$) compared with that at baseline (73.3%; $n=137/187$).

When asked to select between study medication and their previous medication, 74.9% of the patients ($n=125/167$) preferred BAK-free travoprost over previous latanoprost or bimatoprost (25.1%; $n=42/167$; $P < 0.001$). Most patients were “very confident” that they would adhere to their treatment regimen if they were prescribed their preferred medication (84.1%; $n=143/170$) or a medication not associated with burning or stinging (69.4%; $n=118/170$; Figure 3).

Ten patients discontinued BAK-free travoprost preserved with polyquaternium-1 because of 15 AEs (eye irritation, $n=3$; eye pruritus, $n=2$; and eye pain, photophobia, blurred vision, reduced visual acuity, conjunctivitis, eczema around the eye, foreign body sensation, headache, migraine, and dyspnea, $n=1$ each). Serious AEs were reported in four patients (upper gastrointestinal hemorrhage, $n=1$; cholelithiasis, $n=1$; and respiratory infection, $n=2$); all were considered unrelated to BAK-free travoprost. Throughout the study, 50 patients reported 73 treatment-emergent AEs, most of which were reported by $< 2\%$ of patients (Table 2). Approximately, all of these were mild to moderate in severity

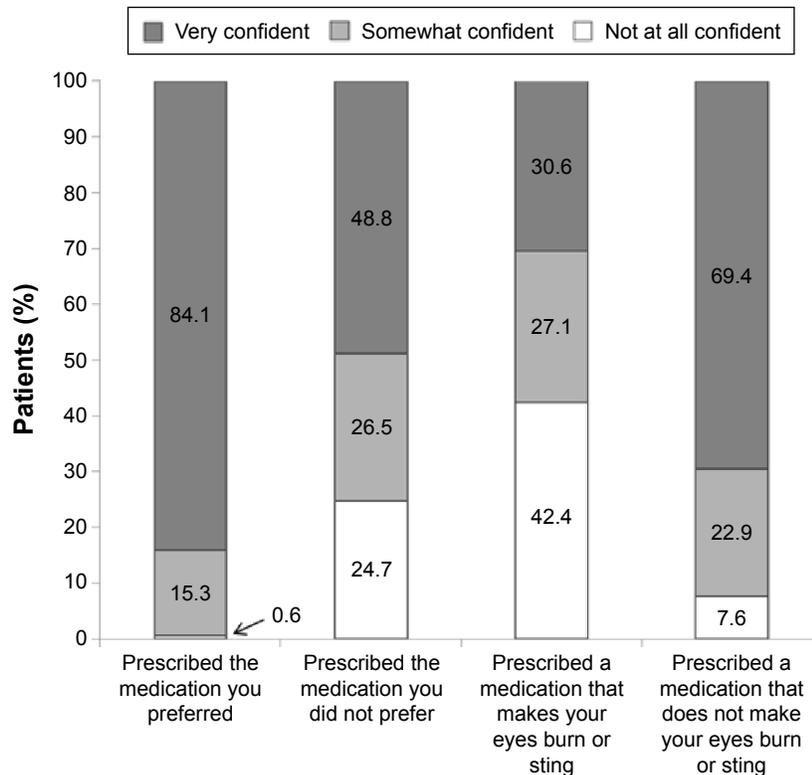


Figure 3 Patient-reported adherence by question category. **Notes:** Patients selected their level of confidence (ie, “not at all confident”, “somewhat confident”, and “very confident”) in answer to the question, “How confident are you that you will use your glaucoma medication as prescribed, if your doctor prescribed the medication?”

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Table 2 Adverse events (safety population)

Parameter, n (%)	BAK-free travoprost (n=199)
Discontinuations due to AEs	10 (5.0)
Discontinuations due to treatment-related AEs ^a	
Serious AEs ^b	4 (2.0)
AE severity	
Mild	59 (29.6)
Moderate	13 (6.5)
Severe	1 (0.5) ^c
AEs (incidence ≥2%)	
Reduced visual acuity	5 (2.5)
Eye pruritus	5 (2.5)
Ocular hyperemia	4 (2.0)
Headache	4 (2.0)

Notes: ^aEye irritation (n=3), eye pruritus (n=2), eye pain (n=1), photophobia (n=1), blurred vision (n=1), reduced visual acuity (n=1), conjunctivitis (n=1), and foreign body sensation (n=1). ^bUpper gastrointestinal hemorrhage (n=1), cholelithiasis (n=1), and respiratory infection (n=2). ^cCholelithiasis.

Abbreviations: AEs, adverse events; BAK, benzalkonium chloride.

(98.6%; n=72/73), and most were considered by the investigators to be unrelated to the study medication (58.9%; n=43/73). A majority of treatment-related AEs were eye disorders (86.7%; n=26/30).

Discussion

AEs associated with few topical glaucoma medications may limit their use and necessitate switching to more tolerable medications.^{26–29} Switching from BAK-preserved latanoprost or bimatoprost to BAK-free, polyquaternium-1-preserved travoprost 0.004% provided additional IOP reductions after 6 weeks of treatment that were maintained for up to 12 weeks. The severity of ocular surface disease was reduced 12 weeks after the transition to BAK-free travoprost. At the end of the study, more patients preferred BAK-free travoprost when asked to select between BAK-free travoprost and BAK-containing latanoprost or bimatoprost. BAK-free travoprost was associated with mild-to-moderate AEs and was generally well tolerated.

Preservatives such as BAK that are commonly used in ophthalmic solutions are associated with burning, stinging, and dry eye and may increase the frequency of punctate keratitis.^{18–20,30–33} Furthermore, increased time of BAK exposure has been associated with a greater incidence of ocular surface disease,³³ suggesting that patients with glaucoma or elevated IOP controlled with a BAK-preserved, IOP-lowering medication may require a therapy switch over time because of BAK-related tolerability concerns.

Persistence and adherence to topical IOP-lowering regimens are low,²⁸ in part because of medication-related side effects;^{26,27,29} thus, improvements in ocular surface symptoms may have a beneficial effect on patients' willingness to take

their medication. Indeed, in the present study, more patients preferred BAK-free travoprost over their previous medication and felt very confident that they would adhere to their treatment if prescribed their preferred medication or a medication that did not elicit ocular symptoms.

Switching to polyquaternium-1-preserved travoprost was associated with IOP reductions from baseline of ~1 mmHg, indicating that it had IOP-lowering efficacy similar to that of the previous treatments of latanoprost or bimatoprost. However, the travoprost formulation maintained IOP reductions while removing the deleterious effects of BAK.

Interpretation of these results is limited by the open-label, single-group study design. Patients may have been more likely to report symptom improvement after transition to BAK-free travoprost preserved with polyquaternium-1 because they anticipated transition to a more tolerable medication. In addition, direct comparison between bimatoprost and latanoprost is not possible because of the forced switch aspect of the study. Finally, the 12-week duration of the study limits long-term efficacy or tolerability extrapolation.

Conclusion

European patients with open-angle glaucoma or ocular hypertension who were switched from BAK-preserved latanoprost or bimatoprost to BAK-free travoprost preserved with polyquaternium-1 because of tolerability concerns experienced additional reductions in IOP and improved ocular symptoms after the switch. Furthermore, when deciding between BAK-free travoprost or BAK-containing latanoprost or bimatoprost, a greater proportion of patients favored BAK-free travoprost preserved with polyquaternium-1.

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Author contributions

All authors meet International Committee of Medical Journal Editors criteria for authorship of this article. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

JG-F has received honoraria and lecture fees from Alcon Laboratories, Inc., Merck, Sharp, & Dohme, Bausch & Lomb, and Novartis and grant support from Alcon Laboratories, Inc., Allergan, Inc., Syntentis, Pfizer, and Merck, Sharp, & Dohme. DAH is an Alcon Laboratories, Inc., employee. The authors report no other conflicts of interest in this work.

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