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CLINICAL STUDY

Travoprost 0.004%/timolol 0.5%-fixed combination with and without benzalkonium chloride: a prospective, randomized, doubled-masked comparison of safety and efficacy

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Abstract

Purpose **The purpose of this study is to compare the safety and intraocular pressure (IOP)-lowering efficacy of travoprost/timolol in a benzalkonium chloride (BAK)-free fixed combination preserved with polyquaternium-1 (TRA/TIM BAK-free), with travoprost/timolol-fixed combination preserved with BAK (TRA/TIM), in patients with open-angle glaucoma or ocular hypertension.**

Methods **In this prospective randomized controlled trial, subjects with IOP of at least 22 mm Hg in one or both eyes at 0900 h, and IOP of at least 21 mm Hg in one or both eyes at 1100 h and 1600 h at two eligibility visits were randomly assigned to receive either TRA/TIM BAK-free ($n = 195$) or TRA/TIM ($n = 193$), dosed once daily in the morning (0900 h) for 6 weeks. IOP was assessed at 0900 h, 1100 h, and 1600 h at each scheduled visit (baseline, 2 and 6 weeks after randomization).**

Results **Mean IOP reduction across all visits and time points was 8.0 mm Hg in the TRA/TIM BAK-free group and 8.4 mm Hg in the TRA/TIM group ($P = 0.0943$). The difference in mean IOP between groups ranged from 0.2 to 0.7 mm Hg across visits and time points, with a mean pooled difference of 0.4 mm Hg (95% CI: −0.1 to 0.8), demonstrating equivalence of the two formulations. The most common drug-related adverse event was hyperemia of the eye (ocular hyperemia and conjunctival hyperemia combined), occurring in 11.8% of the TRA/TIM BAK-free group and 13.0% of the TRA/TIM group.**

Conclusion **Travoprost/timolol BAK-free demonstrated equivalence to travoprost/timolol preserved with BAK in efficacy. No clinically relevant differences in the safety profiles of travoprost/timolol BAK-free and travoprost/timolol preserved with BAK were identified.**

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Keywords: benzalkonium chloride; glaucoma; intraocular pressure; timolol; prostaglandin analogs; travoprost

Introduction

Glaucoma is a common cause of blindness worldwide and its prevalence is increasing.[1,2] Glaucoma and ocular surface disease (OSD) often coexist in the same individuals.[3,4] Interaction between these two conditions may exist. Most topical intraocular pressure (IOP)-lowering medications are preserved with benzalkonium chloride (BAK). Studies comparing the ocular surface effects of ophthalmic solutions, formulated with and without BAK, have consistently shown that tear

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film and corneal surface abnormalities were greater with BAK-containing solutions.[5–12] Consequently, managing glaucoma in patients with co-existing OSD represents a clinical challenge. The need for a multi-drug regimen to adequately control IOP in a significant proportion of patients[13] only compounds this challenge. The need for multiple medications—some of which may require multiple doses per day—further increases BAK exposure.

BAK exposure can be reduced by using preservative-free formulations, BAK-free formulations, or fixed combinations to reduce the number of drops. Several BAK-free IOP-lowering medications are commercially available and have been evaluated in the peer-reviewed literature, including travoprost,[14] two formulations of brimonidine,[15,16] and the dorzolamide—timolol-fixed combination.[17] However, there are currently no BAK-free fixed prostaglandin analog (PGA) combinations available.

Polyquaternium-1 (Polyquad, Alcon Laboratories, Inc., Fort Worth, TX, USA) is a polycationic polymer based on a quaternary ammonium center. Polyquaternium-1 is a commonly used preservative in contact lens solutions, and has been used in a formulation of brimonidine tartrate.[16] In a rat model, polyquaternium-1 exhibited significantly less ocular surface toxicity than BAK.[18]

The fixed combination of travoprost and timolol preserved with BAK (DuoTrav, Alcon Laboratories) is currently approved for use in several world markets, including Canada, Japan, Australia, and several Latin American and European countries, but not in the United States. The purpose of this study was to compare the safety and efficacy of the BAK-free fixed combination travoprost 0.004%/timolol 0.5% preserved with polyquaternium-1 (TRA/TIM BAK-free) to the fixed combination travoprost 0.004%/timolol 0.5% preserved with BAK (TRA/TIM) in patients with open-angle glaucoma or ocular hypertension.

Materials and methods

This manuscript reports the pooled results from two identically designed, randomized, double-masked, multi-center, parallel group clinical trials, one conducted in the United States and the other in Japan. The studies were approved by the relevant institutional review boards at each clinical center, and were conducted in accordance with the tenets of the Declaration of Helsinki. All participating subjects provided written informed consent.

Subjects

Subjects were enrolled from 17 clinical sites in the United States and 14 clinical sites throughout Japan (see appendix for a list of participating centers). Eligible subjects were 20 years of age or older, diagnosed with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension. Eligibility for randomization required subjects to have IOP of at least 22 mm Hg in one or both eyes at 0900 h, and IOP of at least 21 mm Hg in one or both eyes at 1100 h and 1600 h at both eligibility visits; additionally, IOP could be no greater than 36 mm Hg in either eye at any time point on either visit. The same eye had to meet these IOP criteria at each of the three time points at both visits to qualify. Only subjects who could safely discontinue all IOP-lowering therapy for up to 4 weeks during the washout phase were eligible. Subjects were ineligible if they had any form of glaucoma other than open-angle glaucoma or ocular hypertension. Subjects were also ineligible if they had any history or current evidence of any of the following: chronic or recurrent severe ocular inflammatory disease; clinically relevant or progressive retinal disease such as retinal degeneration, diabetic retinopathy, or retinal detachment; any other severe ocular pathology (including severe dry eye) that would preclude the safe administration of a PGA; or severe or serious hypersensitivity to prostaglandin drugs or their analogs, β-blocker drugs, or to any components of the study medications. Other exclusion criteria included history of ocular infection or inflammation or ocular laser surgery within the past 3 months, or history of ocular trauma or intraocular surgery within the past 6 months. Further exclusion criteria included any of the following: any abnormality preventing reliable applanation tonometry; patients with best-corrected visual acuity (BCVA) worse than 0.6 logMAR score; patients with angle grade less than Grade 2 as measured by gonioscopy; patients with a cup/disc ratio greater than 0.80 (horizontal or vertical measurement); patients with severe central visual field loss (defined as a sensitivity of $\leq$10 dB in at least two of the four visual field test points closest to the point of fixation); patients who could not safely discontinue all glucocorticoid medications administered by any route; use of any additional topical or systemic ocular hypotensive medication during the study; history or current evidence of severe, unstable or uncontrolled cardiovascular, hepatic, or renal disease (eg, sinus bradycardia, overt cardiac failure, greater than first degree atrioventricular block, cardiogenic shock, clinically relevant angina, or uncontrolled hypertension) that would preclude the safe administration of a topical β-blocker; history or current evidence of bronchial asthma, or severe chronic obstructive pulmonary disease that would, in the opinion of the investigator, preclude the safe administration of a topical β-blocker; patients with less than 30 days stable dosing regimen before the Screening Visit of any non-IOP-lowering medications or substances administered by systemic route and used on a

chronic basis that could affect IOP; or history of or current hypoglycemia or uncontrolled diabetes. In addition, females of childbearing potential were ineligible to participate if they were currently pregnant or intended to become pregnant during the study period; had a positive urine pregnancy test; were breastfeeding; or were not using a highly effective means of birth control.

Materials

All study medications were supplied in identical white polypropylene bottles. Each bottle was filled to a volume of 2.5 ml of either TRA/TIM BAK-free or TRA/TIM.

Visits

Informed consent was obtained at a screening visit. Automated perimetry and gonioscopy were also performed at the screening visit. A slit lamp examination and assessment of BCVA were performed at 0900 h at all visits. Dilated fundus examination (including retina, macula, choroid, optic nerve head, vitreous, and cup-to-disc ratios) was performed before randomization, and at exit from the study. Eligible participants then discontinued all topical IOP-lowering therapy according to the following schedule: 4 days for miotics and oral/topical carbonic anhydrase inhibitors; 13 days for adrenergic agonists; 27 days for β-blockers and PGAs. After washout, subjects attended two eligibility visits six or more days apart. At these visits, after confirming washout status, and interim medical history and ophthalmic examination, Goldmann applanation tonometry was performed in both eyes at 0900, 1100, and 1600 h. Qualifying subjects were randomized in a 1 : 1 ratio to begin treatment with either TRA/TIM or TRA/TIM BAK-free, dosed once daily at 0900 h in both eyes. Randomization was centralized, and utilized a randomization scheme prepared in advance by Alcon's SAS Programming group. Subjects returned for two on-therapy visits at 2 and 6 weeks after randomization, when they underwent Goldmann tonometry at 0900 h before morning dosing of study medication, followed immediately by instillation of study medication, and subsequently by Goldmann tonometry at 1100 h and 1600 h. Subjects exited the study following the 1600 h assessment at week 6.

Assessments

IOP values at each time point were the mean of two measurements within 4 mm Hg. If the first two measurements differed by more than 4 mm Hg, a third measurement was taken, and the IOP value was the mean of the two closest measurements or of all three, if equally spaced. Safety assessments included adverse events, measurements of pulse and blood pressure, and ocular assessments (visual acuity, slit-lamp examination, and dilated fundus examination). Both solicited and unsolicited adverse events were recorded. In addition, ocular hyperemia was assessed on a scale ranging from 0 (none/trace) to 3 (severe) units in 0.5 unit increments. For each patient, the average score of both eyes at each visit was used for analysis.

Statistical analysis

Data from the two studies were pooled for analysis; the protocols for both studies included the statistical plans of a combined analysis. One eye per subject was analyzed. The primary efficacy hypothesis was that mean IOP, pooled across all visits and time points, would be equivalent in the two treatment groups. Hypothesis testing was conducted using repeated measures analysis of covariance with baseline IOP included as a covariate. For the test of equivalence, a 95% two-sided confidence interval for the difference between treatment groups in mean IOP combined across all visits and time points was constructed, based on the analysis of covariance. The equivalence margin for the primary efficacy hypothesis was 1.5 mm Hg. This criterion is commonly used and accepted in glaucoma studies that evaluate equivalence of a test medication and an active control. Approximately 330 patients were planned to be enrolled in both studies combined (165 per treatment group). With 150 evaluable patients per treatment group, there was more than 90% coverage probability that a 95% two-sided confidence interval would fall within ± 1.5 mm Hg. The sample size estimate was based upon a standard deviation for IOP of 3.5 mm Hg and a 5% chance of a Type I error. Primary inference for the test of equivalence was based upon the per protocol data set, with the intent-to-treat results included as a test of robustness. The data presented in the Results section are from the per protocol data set. The secondary efficacy hypothesis was that the percentage of patients with IOP <18 mm Hg, or IOP percent reduction of $\geq 30\%$, would be equivalent between treatment groups. A repeated measures logistic regression analysis using generalized estimating equations was used to compare the overall treatment group difference. Type I error for this secondary efficacy analysis was controlled at $\alpha = 0.05$. In addition, a 'gate-keeping' strategy was implemented such that the secondary efficacy outcome was deemed relevant only if primary efficacy was first demonstrated.

Results

Overall, 388 patients were enrolled in the two studies and underwent randomization. Pooled demographical

data on subjects by randomization group is presented in Table 1. There were no statistically significant differences between treatment groups for age, race, sex, diagnosis, or iris color. All subjects received at least one dose of study medication and were included in the safety analysis. Five subjects lacked any on-therapy efficacy data and were excluded from the intent-to-treat analysis. An additional 11 subjects were excluded from the per protocol analysis because of protocol violations (including use of excluded concomitant medications in six patients, violation of inclusion criteria in two patients, violation of exclusion criteria in two patients, and noncompliance in one patient), leaving 372 evaluable subjects in the per protocol data set.

Comparison of TRA/TIM BAK-free and TRA/TIM

Mean baseline IOP values ranged from 0.2. to 0.3 mm Hg higher in the TRA/TIM BAK-free group compared with the TRA/TIM group; these differences were not statistically significant (Table 2). The pooled mean IOP difference between TRA/TIM BAK-free and TRA/TIM groups was 0.4 mm Hg (95% CI: −0.1 mm Hg, 0.8 mm Hg), demonstrating equivalence of the two formulations. A similar result was observed in the intent-to-treat analysis. The 95% confidence limits for the difference in mean IOP between TRA/TIM BAK-free and TRA/TIM groups were within ± 1.5 mm Hg at all visits and time points.

Table 1 Subject demographics by treatment group (per protocol data set)

Demographics	*Total*		*TRA/TIM BAK-free*		*TRA/TIM*		P-*Value*
	N	%	N	%	N	%	
Total patients	372	100.0	188	100.0	184	100.0	
Region							
United States	285	76.6	144	76.6	141	76.6	1.0*
Japan	87	23.4	44	23.4	43	23.4	
Age (years)							
<65	174	46.8	86	45.7	88	47.8	0.76*
>65	198	53.2	102	54.3	96	52.2	
Mean ± SD	64.3 ± 11.5		64.6 ± 11.3		64.1 ± 11.7		0.66**
Race							
Japanese	87	23.4	44	23.4	43	23.4	0.70*
Black	61	16.4	35	18.6	26	14.1	
White	218	58.6	107	56.9	111	60.3	
American Indian or Alaska native	1	0.3	0	0.0	1	0.5	
Asian	1	0.3	0	0.0	1	0.5	
Other	4	1.1	2	1.1	2	1.1	
Sex							
Male	159	42.7	81	43.1	78	42.4	0.92*
Female	213	57.3	107	56.9	106	57.6	
Diagnosis							
Ocular hypertension	146	39.2	74	39.4	72	39.1	0.98*
Open-angle glaucoma	218	58.6	110	58.5	108	58.7	
Open-angle glaucoma with pigment dispersion	3	0.8	1	0.5	2	1.1	
Open-angle glaucoma with pseudoexfoliation	5	1.3	3	1.6	2	1.1	
Iris color							
Blue	68	18.3	33	17.6	35	19.0	0.58*
Brown	243	65.3	122	64.9	121	65.8	
Green	17	4.6	7	3.7	10	5.4	
Hazel	44	11.8	26	13.8	18	9.8	

Abbreviations: TRA/TIM BAK-free, travoprost 0.004%/timolol 0.5% BAK-free; TRA/TIM, travoprost 0.004%/timolol 0.5%.
**P*-value from Fisher's exact test.
***P*-value from *t*-test.

Table 2 IOP values at baseline and at all visits and time points in the pooled data set (per protocol data set; $n = 372$)

	Baseline			*Week 2*			*Week 6*			*Combined*			*Pooled*
	0900 h	*1100 h*	*1600 h*	*0900 h*	*1100 h*	*1600 h*	*0900 h*	*1100 h*	*1600 h*	*0900 h*	*1100 h*	*1600 h*	
TRA/TIM BAK-free													
Mean IOP	25.9	25.2	24.5	16.9	17.1	17.1	16.9	17.6	17.1	16.9	17.3	17.1	17.1
Mean IOP change	—	—	—	−8.2*	−8.0*	−7.9*	−8.2*	−7.5*	−7.9*	−8.2*	−7.7*	−7.9*	−8.0*
Mean % IOP change	—	—	—	−32.5*	−31.6*	−31.3*	−32.6*	−29.8*	−31.4*	−32.5*	−30.7*	−31.3*	−31.5*
N	188	188	188	187	188	188	179	180	179	188	188	188	188
TRA/TIM													
Mean IOP	25.8	24.9	24.2	16.7	16.8	16.6	16.6	16.9	16.8	16.7	16.8	16.7	16.7
Mean IOP change	—	—	—	−8.4*	−8.3*	−8.5*	−8.4*	−8.2*	−8.3*	−8.4*	−8.2*	−8.4*	−8.4*
Mean % IOP change	—	—	—	−33.2*	−32.7*	−33.6*	−33.4*	−32.4*	−32.8*	−33.3*	−32.5*	−33.2*	−33.0*
N	184	184	184	183	180	181	176	176	177	183	181	181	183
Difference** (Mean IOP)	0.2	0.3	0.3	0.2	0.3	0.6	0.2	0.7	0.4	0.2	0.5	0.5	0.4
P-value	0.58	0.34	0.23	0.46	0.30	0.05	0.44	0.02	0.19	0.40	0.05	0.07	0.09
Upper 95% CI	0.7	0.8	0.9	0.8	0.8	1.1	0.8	1.2	0.9	0.7	1.0	1.0	0.8
Lower 95% CI	−0.4	−0.3	−0.2	−0.3	−0.3	0.0	−0.3	0.1	−0.2	−0.3	−0.0	−0.0	−0.1

Abbreviations: CI, confidence interval; Combined, results pooled across week 2 and week 6; Pooled, results pooled across all time points for week 2 and week 6; TRA/TIM BAK-free, travoprost 0.004%/timolol 0.5% BAK-free; TRA/TIM, travoprost 0.004%/timolol 0.5%.
*$P < 0.0001$ for comparison to baseline.
**Difference is TRAV/TIM BAK-free minus TRAV/TIM.
Baseline is the average of the two eligibility visits if both values were not missing; otherwise the non-missing value of the two visits was used.
Estimates based on least squares means using repeated measures analysis of covariance. Baseline estimates obtained from separate model.
P-values and confidence intervals were based on repeated measures analysis of covariance.

IOP reduction from baseline

Both TRA/TIM BAK-free and TRA/TIM produced statistically significant and clinically relevant IOP reductions from baseline (Table 2). Baseline mean IOP across time points in the TRA/TIM BAK-free group ranged from 24.5 to 25.9 mm Hg, and on-treatment, mean IOP across visits and time points ranged from 16.9 to 17.6 mm Hg ($P < 0.0001$ for all compared with baseline), with a pooled mean IOP of 17.1 mm Hg ($P < 0.0001$ compared with baseline). Likewise, baseline mean IOP across time points in the TRA/TIM group ranged from 24.2 to 25.8 mm Hg, and on-treatment, mean IOP across visits and time points ranged from 16.3 to 16.9 mm Hg ($P < 0.0001$ for all compared with baseline), with a pooled mean IOP of 16.7 mm Hg ($P < 0.0001$ compared with baseline). The mean IOP reduction pooled across all visits and time points was 8.0 mm Hg in the TRA/TIM BAK-free group and 8.4 mm Hg in the TRA/TIM group. The mean percent IOP change pooled across all visits and time points was −31.5% in the TRA/TIM BAK-free group and −33.0% in the TRA/TIM group.

IOP response analysis

The proportion of patients in each group who achieved IOP reduction of at least 30% from baseline or IOP below 18 mm Hg was determined for each treatment group (Figure 1). Across all visits and time points, the percent of patients who achieved one or both of these IOP responses ranged from 60.0 to 73.3% in the TRA/TIM BAK-free group, and from 66.5 to 72.7% in the TRA/TIM group. Pooling visits and time points, the overall rate at which one or both IOP response endpoints was met was 67.4% in the TRA/TIM BAK-free patients and 70.3% in the TRA/TIM patients ($P = 0.3710$).

Comparison between regions

To evaluate the consistency of outcomes across geographic regions, analysis of the primary efficacy parameter (mean IOP combined across visits and time points) was also conducted separately for the United States and Japanese studies. The pooled mean IOP difference between treatment groups was 0.4 mm Hg (95% CI: −0.1 mm Hg, 0.9 mm Hg) in the United States study, and 0.3 mm Hg (95% CI: −0.6 mm Hg, 1.3 mm Hg) in the Japanese study. In both studies, the 95% confidence limits were within the pre-specified equivalence margin of ±1.5 mm Hg.

Safety results

No safety issues were identified based upon an assessment of BCVA, ocular signs (cornea, iris/anterior chamber, lens, flare, and aqueous inflammatory cells), ocular hyperemia, or funduscopic parameters (retina/macula/choroid, vitreous, optic nerve, cup/disc ratio).

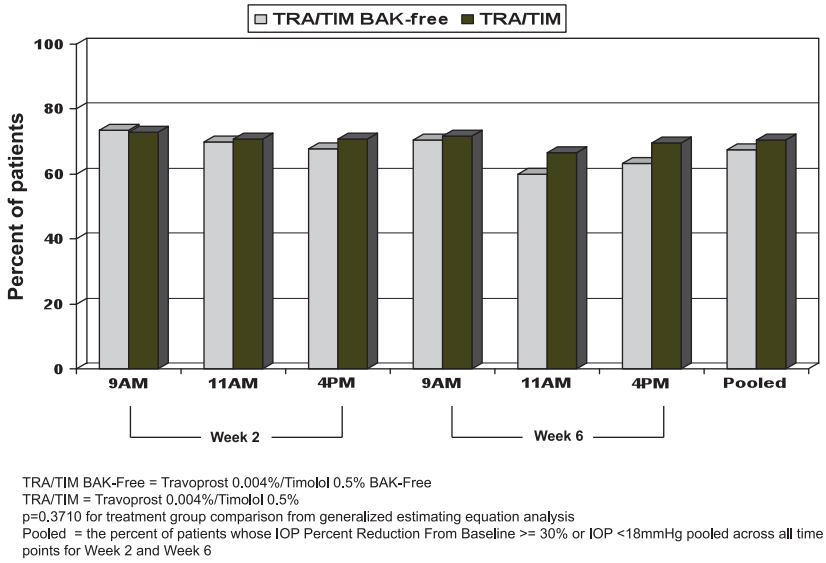

Figure 1 Proportion of subjects achieving ≥30% IOP reduction or IOP < 18 mm Hg by group (per protocol data; $n = 372$).

Table 3 Common ocular adverse drug reactions occurring in ≥1% of subjects by randomization group in the pooled data set ($n = 372$)

Adverse event	*TRA/TIM BAK-free* (n = *195*)	*TRA-TIM* (n = *193*)	*All* (n = *388*)
Ocular hyperemia	17 (8.7)	20 (10.4)	37 (9.5)
Eye irritation	9 (4.6)	11 (5.7)	20 (5.2)
Conjunctival hyperemia	6 (3.1)	5 (2.6)	11 (2.8)
Eye pruritus	6 (3.1)	5 (2.6)	11 (2.8)
Eye pain	4 (2.1)	6 (3.1)	10 (2.6)
Foreign body sensation in eyes	4 (2.1)	5 (2.6)	9 (2.3)
Dry eyes	2 (1.0)	5 (2.6)	7 (1.8)
Photophobia	2 (1.0)	2 (1.0)	4 (1.0)

The most common treatment-related adverse events were hyperemia (ocular and conjunctival; 11.8 and 13.0%) and eye irritation, typically characterized as a mild burning sensation, in 4.6 and 5.7% of the TRA/TIM BAK-free and TRA/TIM groups, respectively (Table 3). Thirteen patients discontinued the study due to adverse events. These included four patients in the TRA/TIM BAK-free group and nine patients in the TRA/TIM group. Eleven of the 13 patients discontinued due to drug-related adverse events, which included eight patients treated with TRA/TIM (hyperemia, eye pain, iritis, photophobia, foreign body sensation, visual acuity reduced) and three patients treated with TRA/TIM BAK-free (hyperemia, meibomianitis). There was one case of treatment-related bradycardia in the TRA/TIM BAK-free group. No statistically or clinically significant alterations of cardiovascular parameters, such as heart rate and blood pressure, were observed in either group.

Discussion

The current study demonstrates that the IOP-lowering efficacy of a BAK-free formulation of travoprost/timolol fixed combination preserved with polyquaternium-1 is equivalent to travoprost/timolol preserved with BAK in patients with open-angle glaucoma or ocular hypertension. The data satisfied the equivalence margin established for this study. This was true for both the United States and Japanese studies separately, as well as the pre-specified analysis of the pooled data set as a whole. The statistically significant differences observed (pooled data) for mean IOP in favor of TRA/TIM at 1600 h at week 2 (0.6 mm Hg) and 1100 h at week 6 (0.7 mm Hg) were deemed to be clinically insignificant.

Both travoprost/timolol BAK-free and travoprost/timolol preserved with BAK provided statistically significant and clinically relevant mean IOP reductions from baseline that were equivalent when combined across study visits, and when pooled across study visits and times. The mean pooled IOP reductions were 8.0 mm Hg for travoprost/timolol BAK-free and 8.4 mm Hg for travoprost/timolol, corresponding to approximately a 33% IOP reduction in each group. All mean reductions were clinically relevant and statistically significant ($P < 0.0001$). These IOP reductions are consistent with the findings of Schuman *et al*[19] in an earlier study of the travoprost/timolol fixed combination, in which IOP reductions with travoprost/timolol were comparable at weeks 2 and 6, as well as month 3; similarly, in a report by Topouzis *et al*[20], travoprost/timolol produced IOP reductions at 2 and 6 weeks that were comparable to 6- and 12-month reductions. Based on these previous reports

demonstrating that maximal IOP reduction is observed at 6 weeks, the current study's relatively short 6-week duration is adequate to characterize maximal IOP reductions with travoprost/timolol.

In addition to producing similar mean IOP reductions, both the BAK-free and BAK-containing formulations of travoprost/timolol produced similar IOP response profiles. Both treatments produced comparable proportions of subjects achieving IOP below 18 mm Hg, or an IOP reduction of 30% or more. Recent clinical trials have demonstrated that achieving IOP reductions of 30% or more, or maintaining IOP consistently below 18 mm Hg, may confer protection against future disease progression.[21–23] In the current study, it was estimated that 67.4% of subjects achieved IOP below 18 mm Hg, or an IOP reduction of 30% or more, in the TRA/TIM BAK-free group, and 70.3% of subjects achieved this in the TRA/TIM group.

The similarity of IOP reduction between BAK-containing and BAK-free formulations of the same IOP-lowering medications has been established by earlier studies of travoprost and other medications. Investigations with timolol have demonstrated that IOP-lowering efficacy is unaffected by reducing[24] or eliminating[25] BAK from the formulation. Lewis *et al*[14] conducted a 3-month randomized clinical trial, comparing the IOP-lowering efficacy of travoprost preserved with and without BAK, and observed equivalent IOP reductions in both groups. Similarly, Gross *et al*[26] conducted a randomized clinical trial demonstrating that travoprost preserved with and without BAK comparably maintained IOP more than 6 mm Hg below untreated baseline for up to 60 h post-dose. These historical reports coupled with the current study demonstrate that BAK may not be essential for the ocular bioavailability of an IOP-lowering agent in maintaining its efficacy profile.

No serious safety issues were identified in patients receiving TRA/TIM BAK-free, based upon a review of adverse events and an assessment of both ocular and cardiovascular parameters in this study. Hyperemia of the eye (ocular hyperemia and conjunctival hyperemia combined) was the most common drug-related adverse event, occurring in 11.8% of subjects in the TRA/TIM BAK-free group, and 13.0% of subjects in the TRA/TIM group. Overall, both the BAK-free and BAK-containing formulations were well tolerated.

These data support that travoprost/timolol BAK-free has comparable IOP-lowering and safety profiles, compared with travoprost/timolol preserved with BAK. Recent and ongoing research suggests that chronic BAK exposure associated with long-term IOP-lowering therapy may have harmful effects on the eye. BAK exposure has been linked to OSD,[5–11] macular edema,[27] and reduced success of glaucoma filtering surgery.[28] BAK induces cytotoxic effects leading to apoptosis in conjunctival cell culture,[29,30] and several studies have demonstrated detrimental effects on both conjunctival and corneal cells in rabbit models.[9–11] This potential interaction between BAK and OSD is clinically relevant, as a recent study estimated that approximately 60% of glaucoma patients have symptoms of OSD.[4] There may be a potential benefit derived from reducing or eliminating BAK exposure in this population.

There are no BAK-free PGA fixed combinations currently available in any global market. This limits the BAK-free therapeutic options for patients requiring multiple IOP-lowering medications. Given that a significant proportion of patients will require more than one medication to achieve adequate IOP control,[13] and the many benefits of fixed combination therapy over concomitant therapy that have been described,[31,32] the absence of BAK-free fixed combination therapies in the marketplace represents an unmet need in glaucoma therapy. Both travoprost and timolol are available in BAK-free formulations in some parts of the world (travoprost Z (Alcon Laboratories) and timolol maleate in preservative-free single-dose vials by various manufacturers); however, a multi-bottle regimen is more complex and less convenient than fixed combination therapy, and may be associated with reduced therapeutic compliance.[33] Thus, there is a need for a BAK-free fixed combination IOP-lowering product so that patients requiring more than a single agent for IOP control can be managed medically without chronic exposure to BAK.

In summary, travoprost/timolol BAK-free demonstrated equivalence to travoprost/timolol preserved with BAK in IOP-lowering efficacy. No clinically relevant differences in the safety profiles of travoprost/timolol BAK-free and travoprost/timolol preserved with BAK were identified. Both mean IOP reductions and the level of IOP control achieved with both formulations are comparable. Travoprost/timolol BAK-free offers the safety and convenience of fixed combination therapy while eliminating exposure of the ocular surface to BAK, thus fulfilling an unmet need in glaucoma management.

Summary

What was known before

- Travoprost 0.004%/timolol 0.5% fixed combination with benzalkonium chloride is approved through much of the world to lower IOP in patients with open-angle glaucoma or ocular hypertension. Benzalkonium chloride exposure can produce ocular surface toxicity.

What this study adds

- Travoprost 0.004%/timolol 0.5% fixed combination with polyquaternium-1 (without benzalkonium chloride) shows equivalence in efficacy to travoprost 0.004%/timolol 0.5% fixed combination with benzalkonium chloride and no safety issues.

Conflict of interest

Dr Y Kitazawa has no proprietary interest in the products discussed in this manuscript, nor has any financial support been received by him from the study sponsor. The other authors are employees of Alcon Laboratories, Inc.

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The study sponsor, Alcon Laboratories, designed the protocol, monitored and collected the data, and performed the statistical analyses. We would like to acknowledge Tony Realini, MD, MPH, for medical writing contributions.

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