Polyquaternium-1–Preserved Travoprost 0.003% or Benzalkonium Chloride–Preserved Travoprost 0.004% for Glaucoma and Ocular Hypertension

JAMES H. PEACE, PETER AHLBERG, MATHIAS WAGNER, JOHN M. LIM, DAVID WIRTA, AND JAMES D. BRANCH

PURPOSE: To demonstrate equivalence of polyquaternium-1–preserved travoprost 0.003% with benzalkonium chloride–preserved travoprost 0.004% in patients with open-angle glaucoma or ocular hypertension.

DESIGN: Double-masked, randomized, 2-treatment, equivalence clinical trial.

METHODS: SETTING: Multicenter clinical trial conducted in 60 centers in the United States and Europe. PATIENT POPULATION: Adult patients with open-angle glaucoma or ocular hypertension. One eye per patient was analyzed. INTERVENTION: Patients were randomized 1:1 to receive polyquaternium-1–preserved travoprost 0.003% (n = 442) or benzalkonium chloride–preserved travoprost 0.004% (n = 422) once daily for 3 months. MAIN OUTCOME MEASURES: Mean intraocular pressure (IOP) was assessed at 8 AM, 10 AM, and 4 PM at week 2, week 6, and month 3. Supportive outcomes were mean and percent IOP change, percentage of patients achieving IOP < 18 mm Hg or ≥30% IOP reduction, and adverse events.

RESULTS: Mean IOP was similar between groups at all study visits (travoprost 0.003% range, 17.5–18.9 mm Hg; travoprost 0.004% range, 17.4–19.0 mm Hg). Mean change (least squares mean differences, −0.1 to −0.3 mm Hg; 95% confidence interval, −0.5 to −0.7 mm Hg) and percentage change (travoprost 0.003%, 28.4%–30.7%; travoprost 0.004%, 28.5%–31.0%) from baseline were comparable. The percentages of patients with IOP < 18 mm Hg and ≥30% reduction of IOP were also similar. Hyperemia was the most frequent treatment-related adverse event with both formulations (travoprost 0.003%, 11.8%; travoprost 0.004%, 14.5%).

CONCLUSIONS: In patients with open-angle glaucoma or ocular hypertension, polyquaternium-1–preserved travoprost 0.003% solution provided equivalent IOP-lowering efficacy to that of benzalkonium chloride–preserved travoprost 0.004%. (Am J Ophthalmol 2015;160(2):266–274. © 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Glaucoma is characterized by optic neuropathy and gradual visual field loss, the latter being a result of retinal ganglion cell atrophy.1 The second-leading cause of blindness worldwide,2 glaucoma is projected to affect approximately 79 million people by 2020.3 Elevated intraocular pressure (IOP) is a leading risk factor for the development of primary open-angle glaucoma, and IOP reduction has been found to slow disease progression.4,5 Treatments to lower IOP include topical ocular hypotensive medications. Prostaglandin analogues are recommended as first-line topical agents because of their IOP-lowering ability, safety profile, and once-daily dosing.6,7 Although not associated with systemic adverse events, prostaglandin analogues may cause local adverse events that can influence adherence and therefore compromise expected treatment outcomes. Hyperemia is the most commonly reported adverse event in patients receiving prostaglandin analogues; adverse effects on appearance (eg, bloodshot eyes) or discomfort associated with hyperemia may diminish compliance with treatment.8,9 TRAVATAN (travoprost 0.004% ophthalmic solution; Alcon Laboratories, Inc, Fort Worth, Texas, USA) is a prostaglandin F2α analogue indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Like many ophthalmic medications, the initial formulation contained the commonly used preservative benzalkonium chloride, which has been associated with conjunctival inflammation,10 tear film disruption,11 and symptoms of ocular surface disease or decreased ocular surface health12,13,14 following chronic exposure. Since its introduction in 2001, efforts have been made to improve

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the safety profile of travoprost 0.004%, and 2 formulations preserved without benzalkonium chloride are currently marketed. Travoprost 0.004% preserved with sofZia (Travatan Z; Alcon Laboratories, Inc) is available in the United States, Canada, and Japan; travoprost 0.004% preserved with polyquaternium-1 (POLYQUAD; Alcon Laboratories, Inc) is marketed throughout most of the world, including Europe, South America, and Asia. Noninferiority of the IOP-lowering efficacy of polyquaternium-1–preserved travoprost 0.004% compared with benzalkonium chloride–preserved travoprost 0.004% was demonstrated in a randomized, double-masked study of 371 patients with open-angle glaucoma or ocular hypertension. Safety profiles of the 2 formulations were generally similar; however, a lower incidence of hyperemia was observed with the polyquaternium-1–preserved formulation. Further improvements in the safety profile of travoprost might be achieved by decreasing the concentration of the active drug and preserving the formulation with an alternative to benzalkonium chloride. To that end, a polyquaternium-1–preserved travoprost formulation with a reduced active drug concentration (0.003% [30 μg/mL]) is being developed for worldwide use; this formulation may confer improvements in overall drug safety while maintaining optimal IOP-lowering efficacy. The aim of the current clinical study was to demonstrate equivalence of travoprost 0.003% preserved with polyquaternium-1 to travoprost 0.004% preserved with benzalkonium chloride in patients with open-angle glaucoma or ocular hypertension.

**METHODS**

- **STUDY DESIGN AND MEDICATIONS**: This was a double-masked, randomized, 2-treatment clinical trial designed to demonstrate equivalence between travoprost 0.003% solution and travoprost 0.004% in adult patients with open-angle glaucoma or ocular hypertension (registered at ClinicalTrials.gov; trial identification number, NCT01453855; trial registry date, October 13, 2011). The study was conducted at clinical sites in the United States, Sweden, Germany, Austria, Spain, and Finland between November 29, 2011 and August 3, 2012. The study protocol received prospective institutional review board (IRB) approval in the United States from Sterling IRB, the Committee for the Protection of Human Subjects, and Western IRB. The protocol also received prospective approval from independent ethics committees in Europe: Regionala Etikprövningsnämnden i Uppsala (Sweden); Ceic Capio Hospital General de Catalunya (Spain); Ethikkommission für das Bundesland Salzburg and Ethikkommission der Medizinische Universität Wien (Austria); Ethik-Kommission Landesärztekammer Rheinland-Pfalz and Ethik-Kommission der Landesärztekammer Brandenburg (Germany); and Pirkanmaan sairaanhoitopiirin etitten toimikunta (Finland). The study was performed in compliance with the Declaration of Helsinki and Good Clinical Practice. Before entering the study, all patients provided written informed consent.

The study consisted of 6 visits conducted during 2 sequential phases: the screening/eligibility phase, which included a screening visit and 2 eligibility visits, and the treatment phase, which included 3 on-therapy follow-up visits conducted at week 2, week 6, and month 3. At screening, patients discontinued use of all pre-study ocular hypotensive medications, and the first eligibility visit was scheduled after a predetermined washout period according to patients’ pre-study medication: miotics and oral/topical carbonic anhydrase inhibitors, >4 days; a and a/β agonists, ≥13 days; β antagonists, prostaglandin analogues, and combination drugs, ≥27 days. For combination drugs comprising ocular hypotensive medications from more than 1 class, the longest washout period for the individual components was used.

Investigators, subinvestigators, all designated IOP operators and readers, patients, the study sponsor, and monitors involved in obtaining, reporting, or reviewing clinical evaluations throughout conduct of the study were masked to treatment. Patient randomization was blocked to ensure a balance of study treatment allocations within investigational sites. The randomization was also stratified by 8 AM baseline IOP (low, 24–27 mm Hg; and high, 28–36 mm Hg) to ensure a balance of treatment groups within each IOP stratum. Upon study entry, patients were assigned screening numbers of 001 to 099 in the appropriate numerical sequence by designated site personnel. The list of patient numbers was generated by statistical personnel not involved in conduct of the study. At the end of the second eligibility visit, eligible patients were randomized in a 1:1 ratio by assigned number and the criteria described above to either polyquaternium-1–preserved travoprost 0.003% or benzalkonium chloride–preserved travoprost 0.004%. An Interactive Web Response System then instructed unmasked study staff which treatment to dispense to patients. Patients were instructed to instill 1 drop of their assigned drug in both eyes once daily at 8 PM (±30 minutes) for 3 months, unless a safety issue prevented instillation in the nonstudy eye. Individual patient treatments were masked until all study data were verified, validated, and locked.

Safety and efficacy variables were assessed at selected time points (8 AM, 10 AM, and 4 PM) during week 2, week 6, and month 3 study visits. One eye from each patient was chosen as the study eye, and only the study eye was used in the efficacy analysis. If only 1 eye of a patient was treated, that eye was selected as the study eye. 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 AM averaged across the 2 eligibility visits. If IOP values were equal at 8 AM, the worse eye was defined as the eye with the higher IOP at 10 AM averaged across the 2 eligibility visits. If values
were equal at 10 AM, the worse eye was defined as the eye
with the higher IOP at 4 PM averaged across the 2 eligi-
bility visits. Finally, if both eyes were equal at 4 PM, the
right eye was selected for analysis.

**PATIENTS:** Patients included men and women aged ≥18
years with a diagnosis of open-angle glaucoma or ocular hy-
pertension. Patients had to have a mean IOP (after washout
of previous treatments) in at least 1 eye of ≥24 mm Hg at
the 8 AM (±30 minutes) time point and ≥21 mm Hg at
the 10 AM (±30 minutes) and 4 PM (±30 minutes)
time points (the same eye). Mean IOP could not be
>36 mm Hg in either eye at any time point.

Patients were excluded if they had a modified Shaffer angle grade <2 in either eye; cup-to-disc ratio >0.8; severe
central visual field loss; chronic, recurrent, or severe inflam-
matory eye disease; intraocular surgery or ocular trauma
within the previous 6 months; ocular infection or inflam-
ination or ocular laser surgery within the previous 3 months;
central corneal thickness >620 μm; best-corrected visual acuity score worse than 55 Early Treatment Diabetic Reti-
opathy Study letters; clinically significant or progressive
retinal disease or other severe ocular pathology; hypersen-
sitivity to prostaglandin analogues; or any abnormality
preventing application tonometry in either eye. Patients
were also excluded if they were unable to discontinue all
IOP-lowering ocular medications before the study.

**OUTCOMES:** The primary efficacy variable was mean IOP
at the week 2, week 6, and month 3 visits, measured at 8
AM, 10 AM, and 4 PM. Supportive efficacy variables
assessed at each visit and time point included mean change
from baseline in IOP, percentage change from baseline in
IOP, proportion of patients with IOP <18 mm Hg, and pro-
portion of patients who achieved ≥30% IOP reduction from
baseline. IOP was measured by Goldmann applanation
tonometry; 2 consecutive IOP measurements were taken
for each eye at all time points. Baseline IOP was deter-
mined by averaging the time-matched measurements
from the 2 eligibility visits; if IOP data were missing for 1
visit, the nonmissing IOP value was used.

Safety variables assessed included solicited and unsolic-
ited adverse events, which were coded using the Medical
Dictionary for Regulatory Activities, version 13.0, and
recorded throughout the study and at each visit. Adverse
events were presented for each treatment group categorized
by severity (mild, moderate, or severe) and relationship to
the study drug.

Ocular hyperemia was evaluated at the second eligibility
visit and the week 2, week 6, and month 3 visits at 8 AM,
10 AM, and 4 PM. Hyperemia assessment was conducted
before IOP measurement or instillation of a tonometry-
disclosing agent. Ocular hyperemia assessments were
made by visual inspection, performed by the same observer
throughout the study, and scored from 0 to 3 in 0.5-unit in-
crements by comparison with a standard set of photographs.

Best-corrected visual acuity (assessed with an Early
Treatment Diabetic Retinopathy Study chart) and ocular
signs (eyelids/conjunctiva, cornea, lens, and iris/anterior
chamber) were evaluated with slit-lamp microscopy at
screening and at the 8 AM time point for every postscreen-
ing study visit. Visual field function testing (standard auto-
mated perimetry) was performed at screening and at 8 AM
at the month 3 visit. Central corneal thickness (measured
with pachymetry) was assessed, and dilated fundus exami-
nation (vitreous, retina, macula, choroid, optic nerve,
and cup-to-disc ratio) was performed at screening and at
4 PM at the month 3 visit.

**STATISTICAL METHODS:** The primary efficacy analysis
was conducted in the intent-to-treat analysis set, defined
as all patients who received study drug and completed at
least 1 scheduled on-therapy study visit. Missing data
were not imputed. The per-protocol analysis set consisted
of all patients who satisfied prerandomization inclusion
and exclusion criteria, received study drug, and completed
at least 1 scheduled on-therapy visit; the per-protocol set
provided supportive data for the primary efficacy endpoint.
Treatment-group differences in mean IOP (the primary ef-
ficacy variable) and mean IOP change from baseline were
examined using a pairwise t test at each time point of
each scheduled on-therapy study visit. Pairwise t tests and
confidence intervals were based on the least squares means
derived from a statistical model that accounted for corre-
lated IOP measurements over time in individual patients
and included baseline IOP stratum and investigational cen-
ter as covariates.

Descriptive statistics were summarized for patient base-
line demographics and IOP at each on-therapy visit
(week 2, week 6, and month 3) and assessment time point
(8 AM, 10 AM, and 4 PM). To conclude equivalence, the
2-sided 95% confidence interval for the difference in IOP
between treatment groups (ie, the mean IOP in the travo-
prost 0.003% solution group minus the mean IOP in the
travoprost 0.004% group) had to be within ±1.5 mm Hg
at each of the 3 assessment time points for each on-
therapy visit. These data were also assessed using a more
stringent criterion of ±1.0 mm Hg. Safety variables were
also summarized using descriptive statistics (eg, frequency
and percentage, or mean change from baseline) as appro-
priate.

Based on an IOP standard deviation of 3.5 mm Hg, a 5%
chance of type I error, and an assumption that the popula-
tion means are identical between groups, a sample size of
320 patients per treatment group was determined to have
≥99% power that the 95% 2-sided confidence interval of
the difference in IOP between groups at any scheduled
on-therapy assessment would fall within ±1.5 mm Hg,
and ≥90% power that the confidence interval would fall
within ±1.0 mm Hg. Target enrollment of 720 patients
was determined to ensure that ≥640 patients (320 per
group) would be followed for 3 months.
RESULTS

- **PATIENTS:** Overall, 864 patients were randomized (travoprost 0.003%, n = 442; travoprost 0.004%, n = 422). Of these, 860 were included in the intent-to-treat population (travoprost 0.003%, n = 442; travoprost 0.004%, n = 418; Table 1); 851 patients were included in the per-protocol population (travoprost 0.003%, n = 436; travoprost 0.004%, n = 415). The study was completed by 432 of 442 patients (98%) in the travoprost 0.003% group and by 408 of 422 patients...

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**TABLE 1.** Baseline Characteristics and Demographics of Patients With Open-Angle Glaucoma or Ocular Hypertension Randomized to Polyquaternium-1–Preserved Travoprost 0.003% or Benzalkonium Chloride–Preserved Travoprost 0.004% (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th></th>
<th>Polyquaternium-1–Preserved Travoprost 0.003% (n = 442)</th>
<th>Benzalkonium Chloride–Preserved Travoprost 0.004% (n = 418)</th>
<th>Total (n = 860)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.4 ± 10.5</td>
<td>65.0 ± 10.9</td>
<td>65.2 ± 10.7</td>
</tr>
<tr>
<td>&lt;65, n (%)</td>
<td>189 (43)</td>
<td>191 (46)</td>
<td>380 (44)</td>
</tr>
<tr>
<td>≥65, n (%)</td>
<td>253 (57)</td>
<td>227 (54)</td>
<td>480 (56)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>316 (72)</td>
<td>307 (73)</td>
<td>623 (72)</td>
</tr>
<tr>
<td>Black</td>
<td>112 (25)</td>
<td>106 (25)</td>
<td>218 (25)</td>
</tr>
<tr>
<td>Asian</td>
<td>11 (3)</td>
<td>4 (1)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
<td>1 (0.2)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>173 (39)</td>
<td>174 (42)</td>
<td>347 (40)</td>
</tr>
<tr>
<td>Female</td>
<td>269 (61)</td>
<td>244 (58)</td>
<td>513 (60)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>130 (29)</td>
<td>121 (29)</td>
<td>251 (29)</td>
</tr>
<tr>
<td>Open-angle glaucoma</td>
<td>304 (69)</td>
<td>290 (69)</td>
<td>594 (69)</td>
</tr>
<tr>
<td>Open-angle glaucoma with pigment dispersion</td>
<td>7 (2)</td>
<td>7 (2)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Open-angle glaucoma with pseudoexfoliation</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Baseline intraocular pressure, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24–27 mm Hg</td>
<td>303 (69)</td>
<td>291 (70)</td>
<td>594 (69)</td>
</tr>
<tr>
<td>28–36 mm Hg</td>
<td>139 (31)</td>
<td>127 (30)</td>
<td>266 (31)</td>
</tr>
</tbody>
</table>

Percentages may not add to 100 because of rounding.

**FIGURE 1.** Disposition of patients with open-angle glaucoma or ocular hypertension receiving polyquaternium-1–preserved travoprost 0.003% or benzalkonium chloride–preserved travoprost 0.004%.
(97%) in the travoprost 0.004% group. Overall, 24 of 864 patients (3%) discontinued early from the study, including 10 (2%) in the travoprost 0.003% group and 14 (3%) in the travoprost 0.004% group (Figure 1). The most common reasons for discontinuation were adverse events (n = 7), inadequate control of IOP (n = 6), and patient decision unrelated to an adverse event (n = 6). Additionally, 3 patients were lost to follow-up. Other reasons for discontinuation were noncompliance (n = 1) and “other” (n = 1).

Within the intent-to-treat population, patients had a mean age of 65 years; most patients were women (n = 513 of 860, 60%) and white (n = 623 of 860, 72%) (Table 1). A majority of patients had a diagnosis of open-angle glaucoma (n = 594 of 860, 69%). Mean baseline IOP measurements for patients receiving travoprost 0.003% or travoprost 0.004% were comparable at 8 AM (26.9 mm Hg and 27.1 mm Hg, respectively), 10 AM (25.4 mm Hg and 25.6 mm Hg), and 4 PM (24.6 mm Hg and 24.8 mm Hg). Baseline IOP measurements across all time points and study drug groups ranged from 21 to 36 mm Hg. Mean corneal thickness at baseline was similar between groups (travoprost 0.003%, 552.9 μm; travoprost 0.004%, 551.8 μm). No substantial differences were observed between groups regarding any demographic parameter or baseline characteristic.

- **Efficacy**: Primary Efficacy Analysis. On-treatment IOP values between the travoprost 0.003% solution group (range, 17.5–18.9 mm Hg) and travoprost 0.004% group (range, 17.4–19.0 mm Hg) were similar (Figure 2). The least squares mean differences in IOP values between the travoprost 0.003% and travoprost 0.004% groups at each time point and study visit ranged from –0.3 to 0.0 mm Hg, with confidence intervals ranging from –0.7

![FIGURE 2. Forest plot showing mean treatment differences in intraocular pressure by visit and time point in patients with open-angle glaucoma or ocular hypertension receiving polyquaternium-1–preserved travoprost 0.003% or benzalkonium chloride–preserved travoprost 0.004% (intent-to-treat population). Data are presented as least squares mean and 95% confidence interval.](image)

<table>
<thead>
<tr>
<th>Study Visit and Time Point</th>
<th>Week 2</th>
<th>Week 6</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>19.4 ± 0.16</td>
<td>19.3 ± 0.16</td>
<td>19.2 ± 0.17</td>
</tr>
<tr>
<td>10 AM</td>
<td>18.6 ± 0.16</td>
<td>18.5 ± 0.16</td>
<td>18.3 ± 0.17</td>
</tr>
<tr>
<td>4 PM</td>
<td>18.0 ± 0.16</td>
<td>18.0 ± 0.16</td>
<td>18.0 ± 0.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polyaquarmine-1–Preserved Travoprost 0.003%</th>
<th>Benzalkonium Chloride–Preserved Travoprost 0.004%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least Squares Mean ± Standard Error</td>
<td>Least Squares Mean ± Standard Error</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Week 2</td>
<td>Week 2</td>
</tr>
<tr>
<td>8 AM</td>
<td>19.4 ± 0.16</td>
</tr>
<tr>
<td>10 AM</td>
<td>18.6 ± 0.16</td>
</tr>
<tr>
<td>4 PM</td>
<td>18.0 ± 0.16</td>
</tr>
</tbody>
</table>
to 0.4 mm Hg (Table 2). Thus, at all 9 assessments, the 95% confidence intervals for the mean differences in IOP between treatment groups were within the prespecified margin of 61.5 mm Hg, indicating statistical equivalence. Furthermore, 95% confidence intervals for mean between-group IOP difference at each time point of all study visits were within an equivalence margin of 61.0 mm Hg. Mean IOP and 95% confidence intervals in the per-protocol data set supported the intent-to-treat data; all 95% confidence intervals were <1.0 mm Hg.

Supportive Efficacy Analysis. Mean changes from baseline in IOP in the travoprost 0.003% group (range, 7.1–8.2 mm Hg) and the travoprost 0.004% group (range, 7.1–8.4 mm Hg) were similar throughout the study (Figure 3). The least squares mean differences in change from baseline in IOP between the 2 treatment groups at each time point of each study visit ranged from /C0.1 to 0.3 mm Hg (95% confidence interval, /C0.5 to 0.7 mm Hg). Mean percentage reductions in IOP from baseline at each time point of each visit were similar in the travoprost 0.003% group (range, 28.4%–30.7%) and travoprost 0.004% group (range, 28.5%–31.0%) and did not vary substantially from week 2 to month 3.

The proportion of patients with IOP values <18 mm Hg or with IOP reduction >_30% was similar between travoprost 0.003% and travoprost 0.004% treatment groups throughout the study (Table 3).

SAFETY: The safety profiles of travoprost 0.003% and travoprost 0.004% were generally similar (Table 4). No serious treatment-related adverse events were reported.
All treatment-emergent serious adverse events were nonocular in nature. Serious adverse events included chest pain (n = 2), viral gastroenteritis (n = 1), pneumothorax (n = 1), abdominal pain (n = 1), lung collapse (n = 1), and unspecified injury (n = 1) in the travoprost 0.003% group and cellulitis (n = 1) in the benzalkonium chloride–preserved travoprost 0.004% group. A trend toward fewer ocular sign changes from baseline was observed for ocular surface or adnexa parameters (eg, changes in eyelids/conjunctiva and cornea) and in anterior chamber inflammation (eg, changes in iris/anterior chamber and aqueous flare/cells) with travoprost 0.003% vs travoprost 0.004%. This difference was due primarily to a slightly higher incidence of changes in eyelids/conjunctiva and cornea with travoprost 0.004% (n = 30 of 442) compared with travoprost 0.003% (n = 21 of 421; 5%).

No meaningful differences in changes from baseline were observed for best-corrected visual acuity, visual field, central corneal thickness, or fundus parameters between treatment groups. A trend toward fewer ocular sign changes from baseline was observed for ocular surface or adnexa parameters (eg, changes in eyelids/conjunctiva and cornea) and in anterior chamber inflammation (eg, changes in iris/anterior chamber and aqueous flare/cells) with travoprost 0.003% vs travoprost 0.004%. This difference was due primarily to a slightly higher incidence of changes in eyelids/conjunctiva in the travoprost 0.004% group (n = 21; 5%) than in the travoprost 0.003% group (n = 13; 3%).

### DISCUSSION

The purpose of this study was to determine whether a new polyquaternium-1–preserved ocular solution containing travoprost 0.003% would offer similar efficacy with improved tolerability compared with a benzalkonium chloride–preserved formulation containing travoprost 0.004%, which represents the concentration in currently marketed travoprost eye drops. Travoprost 0.003% and travoprost 0.004% produced similar IOP reductions through 3 months of treatment, and the criterion for equivalence was met. Treatment-related hyperemia was observed in 12% of patients receiving travoprost 0.003% and in 15% of those receiving travoprost 0.004%. More patients in the travoprost 0.004% group had an increase in hyperemia score greater than 1 unit during treatment; however, safety assessments were not analyzed for statistical significance. With both formulations, maximal IOP-lowering efficacy was achieved after 2 weeks of treatment and was maintained through 3 months.

No patterns emerged over the course of the study that would suggest any patient safety issues with travoprost 0.003% solution or travoprost 0.004%. There were no serious treatment-related adverse events, and patient discontinuations were consistent with previous clinical data associated

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**TABLE 4.** Summary of Treatment-Emergent Adverse Events in Patients With Open-Angle Glaucoma or Ocular Hypertension Receiving Polyquaternium-1–Preserved Travoprost 0.003% or Benzalkonium Chloride–Preserved Travoprost 0.004%

<table>
<thead>
<tr>
<th>Adverse Event Category, N (%)</th>
<th>Polyquaternium-1–Preserved Travoprost</th>
<th>Benzalkonium Chloride–Preserved Travoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>0 (1)</td>
<td>0 (1)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>5 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Treatment-related adverse event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not treatment related</td>
<td>5 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Discontinuations due to an adverse event</td>
<td>3 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related adverse event</td>
<td>2 (0.5)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Non-treatment-related adverse event</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Patients with ≥1 adverse event</td>
<td>134 (30)</td>
<td>136 (32)</td>
</tr>
<tr>
<td>Treatment-emergent adverse events with an incidence ≥5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>31 (7)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>25 (6)</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Patients with ≥1 treatment-related adverse event</td>
<td>79 (18)</td>
<td>80 (19)</td>
</tr>
<tr>
<td>Treatment-related adverse events with an incidence ≥1%</td>
<td></td>
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</tr>
<tr>
<td>Ocular hyperemia</td>
<td>27 (6)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>25 (6)</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>12 (3)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>9 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>6 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>2 (0.5)</td>
<td>4 (1)</td>
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</tbody>
</table>
with travoprost. Overall, most observed cases of hyperemia (90%) were classified as mild, and no meaningful changes in either treatment were reported for visual acuity, visual fields, corneal thickness, and fundus parameters.

Previous reports have described different travoprost and preservative concentrations. A 3-month, double-masked, randomized, parallel group study of patients with open-angle glaucoma or ocular hypertension demonstrated statistical noninferiority of the IOP-lowering efficacy of polyquaternium-1–preserved travoprost 0.004% and benzalkonium chloride–preserved travoprost 0.004%. Safety profiles for the travoprost formulations preserved with polyquaternium-1 vs benzalkonium chloride were generally similar, although a higher incidence of hyperemia was observed in patients receiving travoprost 0.004% preserved with benzalkonium chloride compared with those receiving travoprost 0.004% preserved with polyquaternium-1 (9% vs 6%). In a 6-month, randomized, double-masked trial of travoprost 0.004% and travoprost 0.0015% in patients with open-angle glaucoma or ocular hypertension, patients receiving travoprost 0.004% had lower mean IOP across visits and better IOP control throughout the day compared with patients receiving travoprost 0.0015%. Additionally, more patients receiving travoprost 0.004% vs travoprost 0.0015% achieved IOP reductions ≥25%, with the greatest efficacy difference observed at 4 PM (64.6% vs 45.8%). In contrast, the current study demonstrated that reducing the concentration of travoprost to 0.003% retained IOP-lowering efficacy equivalent to that of travoprost 0.004%. In addition, overall safety profiles were generally similar between the 2 travoprost concentrations; an increase in hyperemia of ≥1 unit from the baseline maximum was observed in

![FIGURE 4. Hyperemia scores in patients with open-angle glaucoma or ocular hypertension receiving polyquaternium-1–preserved travoprost 0.003% or benzalkonium chloride–preserved travoprost 0.004% (safety population). Data are presented as descriptive mean ± standard deviation.](image-url)
of travoprost concentration on hyperemia rates and adverse event profiles. A further limitation is that hyperemia was assessed semi-objectively.

In conclusion, the IOP-lowering efficacy of polyquaternium-1–preserved travoprost 0.003% was equivalent to that of benzalkonium chloride–preserved travoprost 0.004% in this population of patients with open-angle glaucoma or ocular hypertension. The safety profiles of the travoprost 0.003% and travoprost 0.004% solutions were similar.

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REFERENCES


Biosketch

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