# Efficacy and Safety of a Fixed Combination of Travoprost 0.004%/Timolol 0.5% Ophthalmic Solution Once Daily for Open-Angle Glaucoma or Ocular Hypertension

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• PURPOSE: **To compare the efficacy of a fixed combination of travoprost 0.004%/timolol 0.5% every day in the morning with a concomitant regimen of timolol 0.5% every day in the morning, plus travoprost 0.004% every day in the evening; and timolol 0.5% twice daily on the intraocular pressure (IOP) of subjects with open-angle glaucoma or ocular hypertension over 3 months.**

• DESIGN: **Prospective, randomized, double-masked, parallel-group, active-controlled, multicenter trial.**

• METHODS: **Patients comprised adult subjects (n = 403) of either gender with open-angle glaucoma or ocular hypertension in at least one eye. To qualify, the IOP had to be between 22 to 36 mm Hg in the same eye at two consecutive eligibility visits. The primary outcome variable was IOP measured with a Goldmann applanation tonometer.**

• RESULTS: **Mean IOP ranged from 16.2 to 17.4 mm Hg with the combination travoprost/timolol compared with 15.4 to 16.8 mm Hg in the concomitant travoprost + timolol group, from baselines of 23.1 to 25.6 mm Hg and 22.9 to 25.0 mm Hg, respectively. The fixed combination of travoprost/timolol significantly lowered IOP by 7 to 9 mm, similar to the IOP reductions observed with concomitant therapy. The most frequent ocular adverse event was hyperemia that occurred in 14.3% and 23.4% of subjects treated with travoprost/timolol combination and concomitant travoprost + timolol, respectively.**

• CONCLUSIONS: **Travoprost/timolol combination produces greater IOP reductions than the positive control, timolol 0.5%, and reductions that were similar to concomitant travoprost + timolol. This study demonstrates that the fixed combination of travoprost/timolol produces significant and clinically relevant reductions of IOP in a once-daily dosing regimen. (Am J Ophthalmol 2005; 140:242–250. © 2005 by Elsevier Inc. All rights reserved.)**

THE GLAUCOMAS ARE A GROUP OF DISEASES CHARacterized by optic nerve damage and visual field loss. Although elevated intraocular pressure (IOP) is not necessary for damage to occur, it is a major causal risk factor resulting in damage to the optic nerve. β-Adrenergic blocking agents have been used extensively to treat open-angle glaucoma and ocular hypertension, and for years, they were the dominant class of drug used for the treatment of glaucoma.[1,2] β-Blockers reduce IOP by slowing the rate of aqueous humor formation.[3]

Prostaglandin analogues, another class of potent ocular hypotensive substances, reduce IOP by increasing uveoscleral outflow of aqueous humor.[4–7] Travoprost ophthalmic solution, 0.004% (Travatan), administered topically once a day, is approved for treatment of patients with open-angle glaucoma or ocular hypertension. Because of the complementary mechanisms of action, a fixed combination of a prostaglandin analogue and a β-adrenergic blocker in a single formulation may be expected to have an additive effect in lowering IOP in patients with open-angle glaucoma or ocular hypertension.

The purpose of this study was to investigate the efficacy and safety of a fixed combination of travoprost 0.004% and

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timolol 0.5%, preserved with benzalkonium chloride 0.015%, administered once a day in the morning compared with a concomitant regimen consisting of timolol 0.5% administered in the morning and travoprost 0.004% administered in the evening. An active control comparison was also made with a regimen consisting of timolol 0.5% administered twice a day.

This was a prospective, randomized, double-masked, parallel group, multicenter, active-controlled clinical trial.

## METHODS

TWENTY-SEVEN INVESTIGATORS IN THE UNITED STATES conducted this double-masked, randomized, active-controlled trial. Institutional review boards approved the study protocol and the informed consent form. Before enrollment, subjects underwent a process of informed consent. All subject consents signed after April 13, 2003 complied with the U.S. federal Health Information Portability and Accountability Act. The study was conducted in accordance with the Declaration of Helsinki and all appropriate International Conference on Harmonization guidelines. Men and women, age 18 years and older, of any race, diagnosed by an ophthalmologist with either open-angle glaucoma or ocular hypertension confirmed on several visits over a 6-month period, were eligible to participate. Women were eligible to participate if they were postmenopausal, had been surgically sterilized, or used effective birth control measures. Subjects who qualified initially discontinued all ocular hypotensive medication before entering into the eligibility phase of the study. Miotics and carbonic anhydrase inhibitors were discontinued for 5 days, α- and β-adrenergic agonists for 14 days, and β-adrenergic blockers, prostaglandin analogues, and combination drugs for 28 days.

After the washout period, subjects reported for two eligibility visits scheduled 7 ± 1 day apart. At each visit, IOP was measured at 8 AM, 10 AM, and 4 PM. To qualify for the treatment phase of the study, IOP in at least one eye was required to be ≥22 mm Hg at the 8 AM readings (Figure 1). It was necessary that the same eye qualify at the 8 AM examination on both visits and that the IOP not exceed 36 mm Hg in either eye at any of the IOP measurements taken during the eligibility visits. Additionally, subjects were excluded from participation if they had any of the following conditions in either eye: chronic or recurrent inflammatory eye disease, ocular trauma in the last 6 months, ocular infection within the past 3 months, clinically significant or progressive retinal disease, hypersensitivity to components of the study medications, intraocular surgery within the past 6 months, ocular laser surgery within the past 3 months, best-corrected visual acuity worse than 0.6 logarithm of minimal angle of resolution (logMAR) score, extremely narrow or partially closed angle, cup/disk ratio >0.8, history of bronchial asthma, or severe chronic obstructive pulmonary disease. Subjects were not allowed to participate if they could not discontinue the use of glucocorticoid medications or if they were not receiving stable doses of any medication that could affect IOP for 30 days before the beginning of the study.

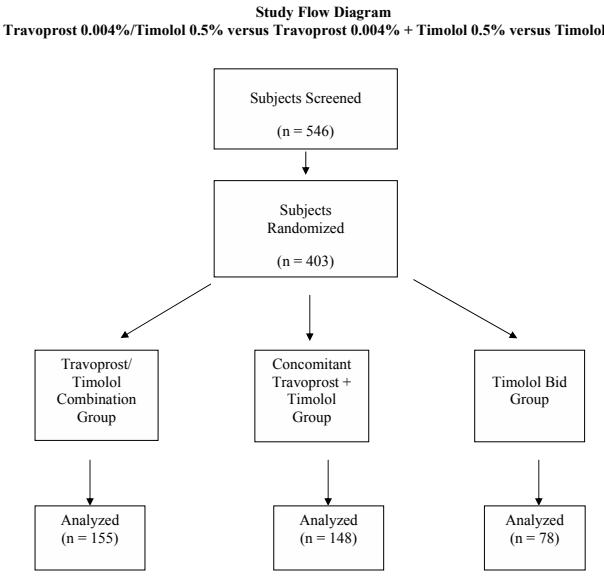



**FIGURE 1. Study flow diagram illustrating travoprost 0.004%/timolol 0.5% vs travoprost 0.004% + timolol 0.5% vs timolol 0.5%.**

Subjects who qualified were assigned the next sequential study number and were given study medication with instructions to instill one drop of study medication in the study eye or eyes at 8 AM each morning from the bottle labeled MORNING and one drop in the study eye or eyes at 8 PM from the bottle labeled EVENING. All study medication was packaged in identical bottles labeled with a computer-generated, randomized subject number and the time for administration. Subsequent visits were scheduled at intervals of 2 weeks, 6 weeks, and 3 months. Subjects were instructed not to take the morning dose of medication on visit days because the medication was to be administered at the study site after the 8 AM IOP measurement.

Subjects were randomized to one of three treatment regimens: (1) a fixed combination of travoprost 0.004%/timolol 0.5% ophthalmic solution, administered at 8 AM each morning and vehicle (placebo) at 8 PM each evening for 3 months (travoprost/timolol); (2) timolol maleate ophthalmic solution, 0.5% USP (Alcon Laboratories, Inc, Fort Worth, Texas, USA) administered at 8 AM each morning and travoprost 0.004% (Travatan; Alcon Laboratories) administered at 8 PM each evening for 3 months (concomitant travoprost + timolol); or (3) timolol maleate ophthalmic solution, 0.5% USP (Alcon Laboratories), administered at 8 AM and 8 PM each day for 3 months (timolol).

Subjects were examined at 8 AM, 10 AM, and 4 PM. At the 8 AM examination, the cornea, lens, iris, and anterior cham-

ber were examined by slit lamp, and any flare or cells were graded and recorded. LogMAR visual acuity (best corrected) was assessed at 8 AM at each visit with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart before IOP measurements or any other examination requiring contact with the eye. IOP was checked at each visit by Goldmann applanation tonometry (calibrated a maximum of 2 months before the first subject was screened). Two individuals (an operator and a reader) performed each IOP measurement. The operator was responsible for operating the slit lamp and the instrument dial while the reader read and recorded the results. At each visit, the subjects were examined for the presence of ocular hyperemia. Ocular hyperemia was assessed by the investigator at each visit and was graded on a scale of 0 to 3, with increments of 0.5. The scoring was made by comparing the hyperemia to a standard set of photographs.[8] Hyperemia was reported as an adverse event only if a subject complained of hyperemia or if the subject discontinued the study as a result of hyperemia. Pachymetry data were not collected in this study.

Achromatic automated perimetry was conducted at baseline and at the month 3 visit with a Humphrey Field Analyzer (HFA I or HFA II) with STATPAC, FASTPAC, SITA-standard or SITA-FAST testing algorithms. Photographs of the iris and eyelashes were taken at the second eligibility visit and at week 6 and month 3 with a digital camera. The photographs were assessed by three independent readers at a centralized reading center at Alcon Laboratories. Photos collected at each study visit were compared with the pre-treatment photographs taken at the second eligibility visit. Photographs were evaluated for changes in iris color and changes in eyelashes (color, thickness, and length). Adverse events were recorded as observed by the investigator or study staff or as reported by the subject. All examiners and readers were masked as to the treatment group of each subject.

The primary efficacy variable was mean IOP at the 8 AM, 10 AM, and 4 PM time points. The sample size estimate of 142 assessable subjects per group is based on a SD for IOP of 3.5 mm Hg and a 5% chance of a type I error. The primary statistical objective was to demonstrate that the fixed combination of travoprost 0.004%/timolol 0.5%, administered once daily in the morning, was equivalent therapy to the regimen of timolol 0.5% administered in the morning and travoprost 0.004% administered in the evening. With 142 assessable subjects per group, there was a 90% coverage probability that a 95% two-sided confidence interval would fall within ±1.5 mm Hg. Similarly to studies by Netland et al., which examined differences based on mean IOP between groups, the upper 95% confidence limit was compared to 1.5 mm Hg.[8] Repeated-measures analysis of variance was used for hypothesis testing. Secondary efficacy variables included differences between treatment groups in mean IOP, change from baseline, and the percentage of subjects with clinically significant responses to treatment. Statistical analyses and summary statistics for efficacy were based on protocol analysis of 387 subjects. Analysis of safety data was based on 403 subjects who received at least one dose of study medication. Analyses were performed by SAS 9.1 for Windows.

## RESULTS

A $\chi^2$ TEST OF INDEPENDENCE (OR FISHER'S EXACT TEST IF one or more expected cell counts were $N < 5$) was used to assess differences between treatment groups. The three treatment groups were comparable with regard to demographic characteristics and baseline IOP (Table 1). The subject population was predominantly white ($P = .3787$), with slightly more women than men ($P = .7773$); the mean age was approximately 62 years ($P = .9243$). The majority of subjects presented with open-angle glaucoma or ocular hypertension, and baseline mean IOPs ranged from 22.9 to 25.6 mm Hg. The only significant difference noted between groups in baseline IOP was at the 8 AM time point, with the IOP in the travoprost/timolol combination group significantly higher than the IOP in the concomitant travoprost + timolol group ($P = .0430$).

The fixed combination of travoprost/timolol administered once a day in the morning produced statistically and clinically significant reduction from baseline in IOP (Figures 2 and 3; Table 2). At all visits and all times, the fixed combination of travoprost/timolol lowered IOP between 7.0 and 8.2 mm Hg. Once-daily administration of the fixed combination lowered IOP for approximately 24 hours, with only slight increases in pressure between 4 PM and 8 AM the next morning.

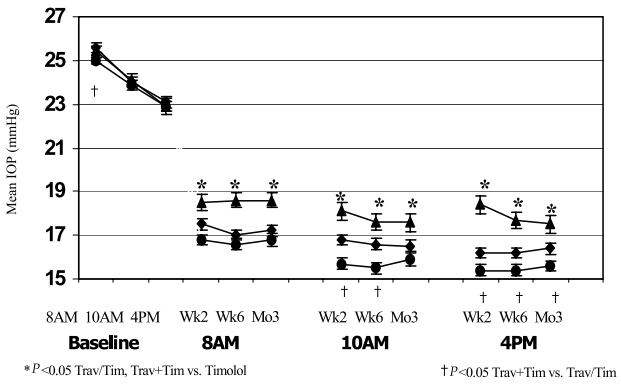
At the three 8 AM time points, there was no statistically significant difference in IOP reduction between the fixed combination travoprost/timolol group (8.2 to 8.6 mm Hg) and the concomitant + timolol group (8.1 to 8.4 mm Hg). The concomitant travoprost + timolol produced slightly greater IOP reductions at the 10 AM (8.0 to 8.4 mm Hg) and 4 PM (7.3 to 7.5 mm Hg) time points (Table 2, Figures 2 to 4). The IOP reductions in the concomitant travoprost + timolol group were statistically superior at five of nine time points compared with the fixed combination travoprost/timolol. Mean differences between travoprost/timolol combination and the concomitant travoprost + timolol group were in the range of ±0.4 to ±1.1 mm Hg. The upper 95% confidence limit of the difference was between 0 and ±1.5 mm Hg in six of nine visits, indicating that the two regimens were similar in efficacy.

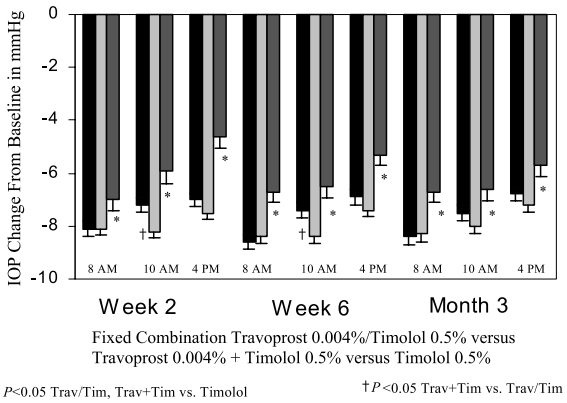
Timolol administered once in the morning and once in the evening was less effective than the two regimens containing travoprost ($P < .02$). Mean differences between groups and 95% confidence intervals are shown in Table 3.

A total of 403 subjects were enrolled onto the study, and all were evaluated for safety. The fixed combination of travoprost/timolol ophthalmic solution administered once a day was safe and well tolerated. The most frequent ocular and non-ocular adverse events related to treatment are

**TABLE 1.** Demographic and Baseline Characteristics by Treatment Group

| Characteristic | Travoprost/Timolol (N = 155) | Travoprost + Timolol (N = 151) | Timolol (N = 81) | *P* Value |
|---|---|---|---|---|
| Age (y) (mean ± SD) | 62.4 ± 10.9 | 61.2 ± 12.7 | 61.8 ± 11.9 | .6807 |
| Gender, n (%) | | | | |
| M | 63 (40.6) | 60 (39.7) | 36 (44.4) | .7773 |
| F | 92 (59.4) | 91 (60.3) | 45 (55.6) | |
| Ethnicity, n (%) | | | | |
| White | 109 (70.3) | 102 (67.5) | 53 (65.4) | .3787 |
| Black | 21 (13.5) | 27 (17.9) | 10 (12.3) | |
| Asian | 2 (1.3) | 0 (0.0) | 0 (0.0) | |
| Hispanic | 23 (14.8) | 20 (13.2) | 17 (21.0) | |
| Other | 0 (0.0) | 2 (1.3) | 1 (1.2) | |
| Iris color, n (%) | | | | |
| Brown | 76 (49.0) | 84 (55.6) | 42 (51.9) | .6864 |
| Hazel | 24 (15.5) | 23 (15.2) | 11 (13.6) | |
| Green | 8 (5.2) | 9 (6.0) | 3 (3.7) | |
| Blue | 45 (29.0) | 35 (23.2) | 23 (28.4) | |
| Gray | 2 (1.3) | 0 (0.0) | 2 (2.5) | |
| Diagnosis, n (%) | | | | |
| Ocular hypertension | 75 (48.4) | 63 (41.7) | 29 (35.8) | .4048 |
| Open-angle glaucoma | 76 (49.0) | 81 (53.6) | 49 (60.5) | |
| Pigmentary glaucoma | 4 (2.6) | 5 (3.3) | 2 (2.5) | |
| Pseudoexfoliation glaucoma | 0 (0.0) | 2 (1.3) | 1 (1.2) | |
| Baseline intraocular pressure (mm Hg) (mean ± SEM) | | | | |
| 8:00 AM | 25.6 ± 2.7 | 25.0 ± 2.1 | 25.4 ± 2.6 | .4994 |
| 10:00 AM | 24.0 ± 2.9 | 23.9 ± 2.8 | 24.1 ± 2.9 | |
| 4:00 PM | 23.1 ± 3.2 | 22.9 ± 2.8 | 22.9 ± 3.4 | |



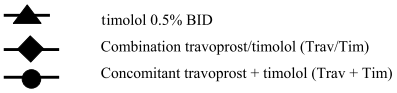




**FIGURE 2. Mean intraocular pressure (IOP) (mm Hg) by treatment group at 8 AM, 10 AM, and 4 PM, travoprost 0.004%/timolol 0.5% vs travoprost 0.004% + timolol 0.5% vs timolol 0.5%. Trav = travoprost; Tim = timolol.**

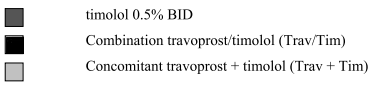



**FIGURE 3. IOP Change from baseline (mm Hg) by treatment group at 8 AM, 10 AM, and 4 PM at each study visit, travoprost 0.004%/timolol 0.5% vs travoprost 0.004% + timolol 0.5% vs timolol 0.5%.**

summarized in Table 4. Most events were reported by the subjects to be mild to moderate in severity and resolved with or without treatment. Hyperemia was the most frequent treatment-related ocular event and was most frequent in the groups receiving travoprost and timolol. No adverse events were reported for changes in iris color or eyelashes during the 3-month study. There were no significant differences noted between the fixed combination of

**TABLE 2.** Mean Intraocular Pressure (IOP), Change from Baseline, and Percentage Change From Baseline*

| Treatment Group | Baseline | | | Week 2 | | | Week 6 | | | Month 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 8 AM | 10 AM | 4 PM | 8 AM | 10 AM | 4 PM | 8 AM | 10 AM | 4 PM | 8 AM | 10 AM | 4 PM |
| Travoprost/timolol | | | | | | | | | | | | |
| N | 155 | 155 | 155 | 155 | 151 | 152 | 142 | 144 | 140 | 144 | 145 | 144 |
| Mean IOP (mm Hg) | 25.6 | 24.0 | 23.1 | 17.4 | 16.8 | 16.2 | 17.0 | 16.6 | 16.2 | 17.2 | 16.5 | 16.4 |
| Mean IOP change (mm Hg) | — | — | — | −8.2 | −7.2 | −7.0 | −8.6 | −7.4 | −6.9 | −8.5 | −7.5 | −6.8 |
| Mean IOP change (%) | — | — | — | −31.7 | −29.6 | −29.7 | −33.2 | −30.5 | −29.2 | −32.9 | −31.0 | −29.1 |
| Travoprost + timolol | | | | | | | | | | | | |
| N | 151 | 151 | 151 | 148 | 145 | 147 | 147 | 145 | 145 | 144 | 142 | 143 |
| Mean IOP (mm Hg) | 25.0 | 23.9 | 22.9 | 16.8 | 15.7 | 15.4 | 16.6 | 15.5 | 15.4 | 16.7 | 15.9 | 15.6 |
| Mean IOP change (mm Hg) | — | — | — | −8.1 | −8.2 | −7.5 | −8.4 | −8.4 | −7.4 | −8.2 | −8.0 | −7.3 |
| Mean IOP change (%) | — | — | — | −32.4 | −34.1 | −32.4 | −33.4 | −34.8 | −32.2 | −32.8 | −33.1 | −31.5 |
| Timolol | | | | | | | | | | | | |
| N | 81 | 81 | 81 | 78 | 77 | 76 | 77 | 77 | 77 | 77 | 77 | 76 |
| Mean IOP (mm Hg) | 25.4 | 24.1 | 22.9 | 18.5 | 18.1 | 18.4 | 18.5 | 17.6 | 17.7 | 18.5 | 17.6 | 17.4 |
| Mean IOP change (mm Hg) | — | — | — | −7.0 | −5.9 | −4.6 | −6.9 | −6.5 | −5.3 | −6.9 | −6.6 | −5.7 |
| Mean IOP change (%) | — | — | — | −27.0 | −24.0 | −19.3 | −26.6 | −26.4 | −22.3 | −26.8 | −26.8 | −23.8 |

Baseline estimates obtained from separate model. Changes from baseline were statistically significant for each treatment group at each time point at each visit ($P < .001$).

*Estimates based on least squares means and confidence intervals from repeated measures analysis of variance.

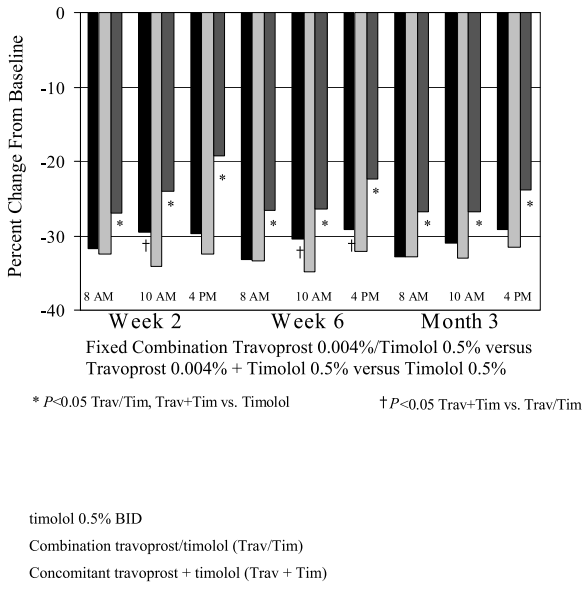



**FIGURE 4. Percentage IOP Change from baseline by treatment group at 8 AM, 10 AM, and 4 PM at each study visit, travoprost 0.004%/timolol 0.5% vs travoprost 0.004% + timolol 0.5% vs timolol 0.5%.**

travoprost/timolol and concomitant travoprost + timolol. Ocular hyperemia was reported in 14.3% of the travoprost/timolol combination subjects and 23.4% of the subjects receiving concomitant travoprost + timolol therapy ($P < .05$). The most frequent ocular event in the group receiving only timolol was ocular discomfort (4.8%).

Bradycardia was the most frequent non-ocular event (4.8%) and occurred only in subjects who received timolol twice a day. Bradycardia was reported as an adverse event if the subject had a clinically relevant reduction in pulse in the opinion of the investigator. Twelve subjects discontinued study medication because of treatment-related adverse events; eight were treated with the fixed combination of travoprost/timolol (hyperemia, photophobia, foreign body sensation; hyperemia, photophobia; foreign body sensation, pruritus; hyperemia; erythema; dyspnea; discomfort; and increased serum glutamic-oxaloacetic transaminase/serum glutamic pyruvic transaminase), and four were treated with concomitant travoprost + timolol (abdominal pain, headache, allergic reaction, and decreased libido). No adverse event resulting in discontinuation of study medication was considered serious.

## DISCUSSION

A VARIETY OF PHARMACOLOGIC THERAPEUTIC AGENTS ARE currently available for the treatment of glaucoma. The aim of therapy is to lower IOP, a major causal risk factor in the progression of the disease.[9–11] Grant and Burke,[11] as well as subsequent work such as the Advanced Glaucoma Intervention Study (AGIS) study,[9] demonstrated a correlation between reducing IOP and preserving visual function. Topical IOP-lowering medications can delay or prevent the onset of primary open-angle glaucoma.[10] IOP-lowering agents from different pharmacologic classes act through distinctly different mechanisms, which allows them to be used either for monotherapy or in combination.

Ophthalmic beta-receptor antagonists have been widely used because of their long duration of action and relatively low side effect profile when used appropriately. These agents lower IOP by decreasing aqueous humor formation in the ciliary process.[3,12,13] Prostaglandin analogues (for example, latanoprost, travoprost, bimatoprost) have recently replaced β-blockers as the most frequently prescribed ocular hypotensive agents available.[14] These agents have been widely adopted for the treatment of glaucoma because of their long duration of action (which permits once-daily dosing), their superior IOP-lowering efficacy relative to beta-receptor antagonists, and their ability to increase uveoscleral outflow.[8,14,15] Studies with HEK cells expressing the cloned human FP receptor, human ciliary muscle, and trabecular meshwork cells report travoprost to be a more potent FP receptor agonist than the other prostaglandin analogues that are commercially available for the treatment of glaucoma.[16–19]

Recent studies involving the concomitant administration of β-blockers and prostaglandin analogues have reported further reductions in IOP over those achieved with either agent dosed as a monotherapy.[20] This may be because beta antagonists decrease aqueous humor production, whereas prostaglandin analogues increase outflow facility.[8,14,15] Therefore, the mechanisms of action of these two agents appear to be complementary. The relative safety of β-blockers and prostaglandin analogues concomitant therapy has been demonstrated.[20] The relatively low side effect profile of these two pharmacologic agents also makes both of them excellent choices for concomitant therapy when used appropriately.

An important factor in the maintenance of adequate IOP control is patient adherence to prescribed treatment. Studies show that as many as 50% of glaucoma patients do not comply with dosing instructions and that dosing frequency and convenience are important factors contributing to patient adherence.[21,22] It is thought within the glaucoma community that simplifying the dosing regimen would result in an increase in patient adherence.[22,23] Tsai and associates[23] used patient questionnaires to identify situational obstacles to medication adherence. They found regimen factors to be an obstacle to adherence for 32% of the glaucoma patients they studied. A dilution effect can be encountered when the patient receives a second medication too quickly after receiving the first medication.[24] Also, side effects can adversely affect patient adherence. Timolol provided twice daily can cause cardiovascular, central nervous system, endocrine, and pulmonary side effects.[25] Therefore, a once-daily travoprost/timolol fixed-combination therapy may have important advantages over a multidose regimen.

**TABLE 3.** Mean Differences in Intraocular Pressure (IOP) and 95% Confidence Intervals (CIs)*

| | Baseline | | | Combined | | | Week 2 | | | Week 6 | | | Month 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Regimen | 8 AM | 10 AM | 4 PM | 8 AM | 10 AM | 4 PM | 8 AM | 10 AM | 4 PM | 8 AM | 10 AM | 4 PM | 8 AM | 10 AM | 4 PM |
| Travoprost/timolol vs timolol | | | | | | | | | | | | | | | |
| Difference | 0.2 | −0.1 | 0.2 | −1.4 | −1.2 | −1.7 | −1.0 | −1.3 | −2.2 | −1.7 | −1.2 | −1.7 | −1.5 | −1.2 | −1.2 |
| Upper 95% CI | 1.0 | 0.7 | 0.9 | −0.7 | −0.5 | −0.9 | −0.1 | −0.5 | −1.3 | −0.9 | −0.3 | −0.8 | −0.7 | −0.3 | −0.3 |
| Lower 95% CI | −0.5 | −0.8 | −0.6 | −2.1 | −2.0 | −2.4 | −1.8 | −2.2 | −3.0 | −2.6 | −2.0 | −2.5 | −2.4 | −2.1 | −2.0 |
| *P* value | .5715 | .8467 | .6691 | .0002 | .0011 | <.0001 | .0249 | .0025 | <.0001 | .0001 | .0080 | .0002 | .0006 | .0074 | .0085 |
| Travoprost + timolol vs timolol | | | | | | | | | | | | | | | |
| Difference | −0.4 | −0.2 | −0.1 | −1.9 | −2.2 | −2.4 | −1.6 | −2.4 | −2.9 | −2.1 | −2.2 | −2.4 | −2.0 | −1.9 | −2.0 |
| Upper 95% CI | 0.3 | 0.6 | 0.7 | −1.1 | −1.4 | −1.7 | −0.7 | −1.6 | −2.0 | −1.2 | −1.3 | −1.5 | −1.1 | −1.0 | −1.1 |
| Lower 95% CI | −1.2 | −0.9 | −0.8 | −2.6 | −2.9 | −3.2 | −2.4 | −3.3 | −3.8 | −2.9 | −3.1 | −3.3 | −2.8 | −2.7 | −2.9 |
| *P* value | .2632 | .6903 | .8285 | .0002 | <.0001 | <.0001 | .0134 | <.0001 | <.0001 | .0005 | <.0001 | <.0001 | .0009 | .0004 | .0001 |
| Travoprost/timolol vs travoprost + timolol | | | | | | | | | | | | | | | |
| Difference | 0.7 | 0.1 | 0.2 | 0.5 | 0.9 | 0.8 | 0.6 | 1.1 | 0.8 | 0.4 | 1.0 | 0.7 | 0.4 | 0.7 | 0.8 |
| Upper 95% CI | 1.3 | 0.7 | 0.9 | 1.1 | 1.5 | 1.4 | 1.3 | 1.8 | 1.5 | 1.1 | 1.7 | 1.5 | 1.2 | 1.4 | 1.6 |
| Lower 95% CI | 0.0 | −0.6 | −0.4 | −0.2 | 0.3 | 0.2 | −0.1 | 0.4 | 0.0 | −0.4 | 0.3 | 0.0 | −0.3 | −0.1 | 0.1 |
| *P* value | .0430 | .8041 | .4394 | .1390 | .0030 | .0130 | .1011 | .0026 | 0.382 | .3425 | .0056 | .0433 | .2288 | .0695 | .0236 |

*Estimates based on least squares means and CIs from repeated measures analysis of variance. Baseline estimates obtained from separate model.

**TABLE 4.** Most Frequent Ocular and Non-ocular Treatment-Related Adverse Events

| Event | Travoprost/Timolol (N = 161) | Travoprost + Timolol (N = 158) | Timolol (N = 84) |
|---|---|---|---|
| Ocular adverse events, n (%) | | | |
| Hyperemia | 23 (14.3) | 37 (23.4) | 2 (2.4) |
| Ocular discomfort | 16 (9.9) | 12 (7.6) | 4 (4.8) |
| Foreign body sensation | 10 (6.2) | 7 (4.4) | 2 (2.4) |
| Pruritus | 7 (4.3) | 8 (5.1) | 0 (0.0) |
| Dryness | 5 (3.1) | 4 (2.5) | 1 (1.2) |
| Keratitis | 2 (1.2) | 5 (3.2) | 0 (0.0) |
| Cells | 3 (1.9) | 3 (1.9) | 2 (2.4) |
| Non-ocular adverse events, n (%) | | | |
| Bradycardia | 0 (0.0) | 0 (0.0) | 4 (4.8) |
| Malaise | 0 (0.0) | 3 (1.9) | 0 (0.0) |
| Headache | 0 (0.0) | 2 (1.3) | 0 (0.0) |
| Rhinitis | 0 (0.0) | 3 (1.9) | 0 (0.0) |
| Taste perversion | 0 (0.0) | 2 (1.3) | 0 (0.0) |

Minimizing the costs associated with glaucoma therapy is another important consideration in successful treatment of the disease. Due to a reduced frequency of dosing, the newer generation products such as the prostaglandin analogues are similar in cost/day in many cases to the early generation compounds.[26,27] The costs of a fixed combination product are expected to be lower than purchasing each product separately. For example, Cosopt therapy was shown to be less costly than separate bottles of dorzolamide and timolol. In a managed care setting, decreasing the number of prescriptions needed would also reduce the number of required co-payments. The reduction in cost of glaucoma therapy may positively contribute to patient satisfaction and therefore adherence.

The results of the current study shows that the fixed combination of travoprost/timolol produces greater IOP reductions than the positive control, timolol 0.5%, which was administered twice daily. The fixed combination of travoprost/timolol significantly lowers IOP by 7 to 9 mm Hg, which is a 29% to 33% reduction relative to an average baseline value of 24 mm Hg. In addition, the fixed combination of travoprost/timolol decreased diurnal mean IOP similarly to the concomitant travoprost + timolol therapy with differences in mean IOP ranging from 0.4 to 1.1 mm Hg. The travoprost/timolol combination lowered IOP up to 8.6 mm Hg. Reductions of IOP were greater with the travoprost/timolol combination at the 8 AM time point; the concomitant travoprost + timolol produced greater IOP lowering at the 10 AM and 4 PM time points. In a study comparing the efficacy of a fixed combination of latanoprost and timolol, Xalcom, to the concomitant dosing of latanoprost and timolol, the difference in mean within-patient diurnal IOP levels was 1.1 mm Hg, favoring the unfixed, concomitant dosing.[28] Interestingly, a phase 3 clinical trial demonstrated greater IOP reductions with concomitant dorzolamide and timolol compared with the fixed combination dorzolamide/timolol drop (Cosopt, Merck & Co, Inc, Whitehouse Station, New Jersey, USA); however, additional phase 4 studies found that the fixed combination had better efficacy.[29–33] Increased efficacy in a fixed-combination product may be attributable to factors such as increased adherence and decreased washout from an inadequate amount of time between dosing separate agents.[24,32] Serle and associates[34] demonstrated that IOP is adversely affected if patients do not wait at least 2 minutes between the application of two topical ocular medications. The travoprost/timolol fixed-combination drop may provide the benefits of better adherence, reduced cost compared with concomitant therapy, and improved side effect profile.[24] The current study demonstrates that the fixed combination of travoprost/timolol produces marked reductions of IOP in a once-daily dosing regimen.[26,27]

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## Biosketch

Joel S. Schuman, MD, is the Eye and Ear Foundation Professor and Chairman of Ophthalmology, at the Eye and Ear Institute, University of Pittsburgh School of Medicine, and Director of the University of Pittsburgh Medical Center (UPMC) Eye Center. He is also Professor of Bioengineering at the University of Pittsburgh.

Dr. Schuman received his medical degree from Mount Sinai School of Medicine in New York City, served his ophthalmology residency at the Medical College of Virginia in Richmond, and completed a 2-year clinical fellowship in glaucoma at the Howe Laboratory of Ophthalmology in Boston, part of Harvard Medical School's Massachusetts Eye and Ear Infirmary, whose faculty he joined in 1990.

He co-founded the Tufts University School of Medicine's–New England Eye Center in 1991, and has been professor and vice chair at Tufts University School of Medicine, and director of the Glaucoma and Cataract Service of the New England Eye Center at Tufts–New England Medical Center in Boston. Dr. Schuman was a member of the Tufts University School of Medicine faculty from 1991 to 2003, and he was also a research professor of electrical engineering and computer science at Tufts University's main campus in Medford, Massachusetts.

Dr. Schuman and his colleagues were the first to identify a molecular marker for human glaucoma, as published in *Nature Medicine*. He is principal investigator of a National Institutes of Health (NIH) grant to study novel glaucoma diagnostics, and is co-investigator of NIH grants for research into novel optical diagnostics and short pulse laser surgery and for advanced imaging in glaucoma. His other research interests include ocular imaging, laser-tissue interactions, aqueous outflow, and clinical pharmacology.

Dr. Schuman has published more than 120 peer-reviewed scientific journal articles, has authored or edited five books, and has contributed numerous book chapters. He also has an interest in CD-ROM presentation of scientific information and

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In 2002, Dr. Schuman received the Alcon Research Institute Award, as well as the New York Academy of Medicine's Lewis Rudin Glaucoma Prize. In 2003, he received the Senior Achievement Award from the American Academy of Ophthalmology. In 2004, he was elected into the American Society for Clinical Investigation.