The Safety and Efficacy of Travoprost 0.004%/ Timolol 0.5% Fixed Combination Ophthalmic Solution

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• PURPOSE: To compare the safety and intraocular pressure (IOP)-lowering efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution (Trav/Tim) to its components travoprost 0.004% ophthalmic solution, TRAVATAN, (Trav) and timolol 0.5% ophthalmic solution (Tim) in patients with open-angle glaucoma or ocular hypertension.

• DESIGN: Randomized multicenter, double-masked, active-controlled, parallel group study.

• METHODS: Two hundred sixty-three patients with open-angle glaucoma or ocular hypertension were randomized to receive Trav/Tim once daily AM (and vehicle PM), Trav once daily PM (and vehicle AM), or Tim twice daily (AM and PM). Efficacy and safety were compared across treatment groups over 3 months.

• RESULTS: Trav/Tim produced a mean IOP decrease from baseline of 1.9 mm Hg to 3.3 mm Hg more than Tim, with a significant decrease in mean IOP at each of the nine study visits ($P \leq .003$). Trav/Tim decreased mean IOP by 0.9 mm Hg to 2.4 mm Hg more than Trav, with a significant decrease in mean IOP at seven of the nine study visits ($P \leq .05$). The adverse event profile for Trav/Tim was comparable to Trav or Tim alone.

• CONCLUSIONS: Over the 3 months of treatment, Trav/Tim produced clinically relevant IOP reductions in patients with open-angle glaucoma or ocular hypertension that were greater than those produced by either Trav or Tim alone. The clinical results that Trav/Tim was safe and well tolerated with an incidence of adverse events was comparable to the results of Trav or Tim alone. Trav/Tim provides both more effective IOP reduction than its components and the benefits of once-daily dosing. (Am J Ophthalmol 2005;140:1–7. © 2005 by Elsevier Inc. All rights reserved.)

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GLAUCOMA IS A GROUP OF OCULAR DISEASES characterized by optic nerve damage and visual field loss. While the precise pathophysiology is unknown, the end result of glaucoma is retinal ganglion cell death. Glaucoma may produce few symptoms and up to 40% of the retinal ganglion cells may die before patients notice any defects in their visual fields.[1] Extensive optic nerve injury and visual field loss often have already occurred by the time of diagnosis. Although some glaucoma patients have normal intraocular pressures (IOPs), glaucomatous injury is highly correlated with increased IOP.[2] Therefore, reducing IOP is a mainstay of glaucoma therapy.

Topical β-adrenergic blocking agents, such as timolol, have been widely accepted as first-line therapy for glaucoma and ocular hypertension.[1,3] β-Blockers reduce IOP by slowing the rate of aqueous humor formation.[4] While β-blockers provide excellent reductions in IOP, they are known to cause cardiovascular and respiratory side effects in some patients.

In recent years, a new family of drugs, the prostaglandin analogues, has become increasingly popular. Studies have shown that travoprost 0.004% ophthalmic solution (Trav; TRAVATAN, Alcon Laboratories, Inc., Fort Worth, Texas) is a potent FP receptor agonist in human ciliary muscle and trabecular meshwork cells.[5,6] Unlike β-blockers, prostaglandin analogs reduce IOP by increasing both uveoscleral (pressure insensitive) and conventional (pressure sensitive) aqueous humor outflow.[7,8] Travoprost is a prostaglandin analog product approved for once-daily dosing in patients with open-angle glaucoma or ocular hypertension. Trav has been shown in previous large-scale, multicenter clinical trials to produce clinically

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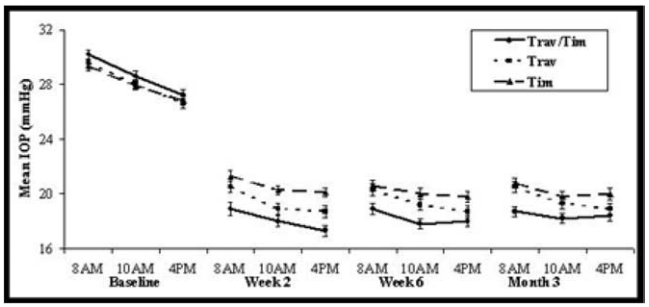

FIGURE 1. Mean intraocular pressure (IOP; mm Hg) for patients on travoprost 0.004%/timolol 0.5%, travoprost 0.004% (Trav), or timolol 0.5% (Tim) therapy. Treatment with Trav/Tim produced a lower mean IOP (±SEM) at each on-therapy visit than either Trav or Tim alone.

relevant reductions of baseline IOP that are better than timolol with a safety profile comparable to other prostaglandin analogs.[9,10]

Still, as many as 40% of patients treated for glaucoma are unable to achieve adequate control of IOP with a single medication.[11] Patients are often prescribed multiple medications from the different classes of IOP-lowering therapies, including carbonic anhydrase inhibitors and α-agonists, in addition to β-blockers and prostaglandin analogs, to help maintain adequate control of IOP. While multiple medications can achieve acceptable IOP levels for many patients, the use of more than one dosing bottle is associated with several concerns, including increased preservative exposure of multiple drops, greater patient costs for multiple prescriptions, reduced compliance, and potential washout from multiple dosing.[12–15]

The complementary mechanisms of action of a prostaglandin analog and a β-blocker are likely to produce a lower IOP in combination when compared with either single agent. Providing a fixed combination in a single formulation may also reduce or eliminate many of the concerns that are associated with a concomitant dosing regimen using separate bottles. The purpose of this study was to evaluate the safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution (Trav/Tim) dosed once daily in the morning compared with monotherapy with either travoprost 0.004% ophthalmic solution dosed once daily in the evening or timolol 0.5% ophthalmic solution (Tim) dosed twice-daily.

PATIENTS AND METHODS

• **STUDY DESIGN:** Thirty-three investigators at 33 U.S. sites conducted this double-masked, randomized active-controlled trial. The study protocol and informed consent document were approved by a central institutional review board, or by the site's local institutional review board. Before enrollment, patients underwent a process of informed consent. Furthermore, all patient consents signed after April 13, 2003 complied with the U.S. Federal Health Information Portability and Accountability Act (HIPAA). The study was conducted in accordance with the Declaration of Helsinki and all appropriate International Conference on Harmonization guidelines.

Adult patients aged 18 years and above of either gender or any ethnicity diagnosed with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension, confirmed on multiple visits over a 6-month period, were eligible for screening. Patients had to be able to discontinue all ocular hypotensive medications at screening to allow for measurement of baseline IOP. The washout period was 5 days for miotics and oral or topical carbonic anhydrase inhibitors, 14 days for α- and β-adrenergic agonists, and 28 days for β-adrenergic blockers, prostaglandin analogs, and the dorzolamide-timolol fixed combination. Patients who met IOP entry criteria at two separate eligibility visits were eligible to be randomized. IOP entry criteria included baseline mean IOP $\geq$ 26 mm Hg at 8 AM, $\geq$ 24 mm Hg at 10 AM, and $\geq$ 22 mm Hg at 4 PM on the first eligibility visit, and IOP $\geq$ 26 mm Hg at 8 AM on the second eligibility visit. Patients must have met each IOP qualification in at least one eye (the same eye for all visits) to be eligible for randomization. Furthermore, patients with a mean IOP of more than 36 mm Hg at any visit during the screening phase were excluded.

Other exclusion criteria included any form of glaucoma other than open-angle glaucoma or ocular hypertension; history of severe chronic, recurrent, or progressive eye diseases (for example, uveitis, progressive age-related macular degeneration); recent therapy with another investigational agent; hypersensitivity to any component 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; cup/disk ratio greater than 0.8; severe central visual field loss with a sensitivity $\leq$ 10 db in at least two of the four visual field test points closest to the point of fixation; history of bronchial asthma or severe chronic obstructive pulmonary disease; or severe, unstable, or uncontrolled cardiovascular, hepatic, renal, or pulmonary diseases. Additionally, patients were requested to discontinue use of all IOP-lowering ocular medications (for 5 to 28 days as noted above) and glucocorticoid medications (regardless of delivery method) for a minimum of 2 weeks. Patients had to be on a 30-day stable-dosing regimen of any additional topical or systemic medications that affect IOP (for example, oral β-blockers) before entry in the study. Women were excluded if they were pregnant or breast-feeding or had the potential to become pregnant while participating in the study.

TABLE 1. Demographic Characteristics of Patients in the Travoprost 0.004%/Timolol 0.5% Fixed Combination Ophthalmic Solution Study

Parameter	n	Trav/Tim	Trav	Tim	*P* Value*
Gender					
Male	126	37	45	44	.5368
Female	132	45	39	48	
Ethnicity					
White	165	52	53	60	.9612
Black	60	18	21	21	
Asian	2	0	1	1	
Hispanic	31	12	9	10	
Iris color					
Brown	138	44	48	46	.7189
Hazel	35	13	12	10	
Green	11	5	2	4	
Blue	72	20	21	31	
Gray	2	0	1	1	
Diagnosis					
Ocular hypertension	80	33	20	27	.0865
Open-angle glaucoma	174	49	63	62	
Pigmentary glaucoma	2	0	0	2	
Pseudoexfoliation	2	0	1	1	
Glaucoma					

Tim = timolol 0.5%; Trav = travoprost 0.004%; Trav/Tim = Travoprost 0.004%/Timolol 0.5% fixed combination.
*Pearson's χ^2 or Fisher's exact test, if needed.

Patients who qualified were randomized into one of three treatment groups in a 1:1:1 fashion. Treatment assignment was computer generated and the investigator was instructed to assign patient numbers sequentially at each site. Patients received either Trav/Tim in the morning plus vehicle in the evening, Trav in the evening plus vehicle in the morning, or Tim in the morning and evening. All study medications were supplied in identical opaque syndiotactic polypropylene oval bottles and clearly labeled as either morning or evening. Patients were provided with both bottles and instructed to dose with one drop from the appropriate bottle at approximately 8 AM (morning dose) and 8 PM (evening dose). Treatments were randomly assigned with both the patient and the investigator masked to the assignment to limit bias. For the same reason, the study required all IOP assessments by Goldmann applanation tonometry to be made by a separate operator and reader. Two consecutive IOP measurements were taken for each eye and the mean IOP was recorded. If the two measurements for the same eye differed by more than 4 mm Hg, a third measurement was taken and the IOP measurements closest to each other were averaged. If the three measurements differed by equal amounts, then all three readings were averaged.

• **STUDY VISITS:** Baseline information was obtained at the screening and eligibility visits. General demographic information, medical and ocular history, visual fields, gonioscopy (if not performed within the last 6 months) and dilated fundus examination of vitreous, retina, macula, and choroid, and optic nerve were performed at screening. Baseline ocular hyperemia; pulse and blood pressure; best-corrected logMAR visual acuity; grading of eyelids and conjunctiva, cornea, lens, aqueous cells, and flare; and iris/eyelash photography were conducted at the second eligibility visit. Mean IOP was measured at screening and at both eligibility visits. Study visits occurred at 2 weeks, 6 weeks, and 3 months after randomization on the second eligibility visit day. The following procedures were performed at all study visits:

- IOP measurement at 8 AM, 10 AM, and 4 PM
- Ocular hyperemia assessment at 8 AM, 10 AM, and 4 PM
- Pulse and blood pressure measurement at 8 AM and 10 AM
- LogMAR visual acuity measurement (best corrected) at 8 AM
- Slit-lamp examination, including evaluation of eyelids and conjunctiva, cornea, lens, and aqueous cells, and flare at 8 AM

Additionally, dilated fundus examinations of vitreous, retina, macula, choroid, optic nerve, and visual field tests were performed at the 3-month visit. Photographs of the iris and eyelashes were taken at the second eligibility visit and at the 6-week and 3-month visits with a digital camera (Sony, CD Mavica MVC-CD400, New York, New York). The photographs were assessed by three independent readers at a centralized reading center at Alcon Laboratories, Inc., Fort Worth, Texas. Photographs 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).

• **DATA ANALYSIS:** The primary efficacy outcome was mean IOP at 8 AM, 10 AM, and 4 PM compared with the baseline values of the intent-to-treat data set. Hypothesis tests were performed using repeated measures analysis of variance. Descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percentage change from baseline. Mean IOP change from baseline was estimated using a repeated measures analysis of variance. With 75 evaluable subjects/treatment group, there is over a 90% power to detect a difference of 2.0 mm Hg between treatments. This estimate is based on a standard deviation for IOP of 3.5 mm Hg and a two-sample *t* test conducted at a 5% chance of a type I error.

Patient safety was evaluated from collection of adverse events, both volunteered by the patient and elicited from study staff. Clinically significant changes in a patient's general medical and ocular health, regardless of the per-

TABLE 2. Summary of Mean IOP ± SD (mm Hg) for Patients on Travoprost 0.004%/Timolol 0.5%, Travoprost 0.004%, or Timolol 0.5% Therapy

Visit	Trav/Tim (n = 82)	Trav (n = 84)	Tim (n = 92)
Baseline*			
8 AM	30.2 ± 2.7	29.6 ± 2.8	29.3 ± 2.6
10 AM	28.6 ± 3.3	28.0 ± 3.1	27.9 ± 3.0
4 PM	27.2 ± 3.5	26.6 ± 3.6	26.8 ± 3.0
Week 2			
8 AM	18.9 ± 4.4	20.5 ± 3.9	21.3 ± 3.6
10 AM	18.0 ± 3.7	18.9 ± 3.7	20.3 ± 3.1
4 PM	17.3 ± 3.5	18.7 ± 3.8	20.1 ± 3.1
Week 6			
8 AM	18.9 ± 3.8	20.3 ± 4.0	20.6 ± 3.4
10 AM	17.8 ± 3.4	19.2 ± 3.6	20.0 ± 3.7
4 PM	18.0 ± 3.5	18.7 ± 3.8	19.8 ± 3.9
Month 3			
8 AM	18.7 ± 3.4	20.5 ± 3.9	20.8 ± 3.3
10 AM	18.2 ± 3.1	19.3 ± 3.7	19.8 ± 3.6
4 PM	18.4 ± 3.7	18.9 ± 3.6	20.0 ± 4.0

IOP = intraocular pressure; Tim = timolol 0.5%; Trav = travoprost 0.004%; Trav/Tim = Travoprost 0.004%/Timolol 0.5% fixed combination.

*Baseline IOP was the average IOP of the two eligibility visits in the patients' worse eye.

ceived relationship to study medication by patient or investigator were collected as adverse events. Additionally, the following study assessments were used to determine clinically significant changes as determined by the investigator: ocular hyperemia, cardiovascular parameters, visual acuity, slit-lamp and dilated fundus examinations, and iris/eyelash photography compared with baseline values. Adverse events were evaluated for potential relationship to study medication by the investigator and by an independent ophthalmologist who also was masked to the treatment randomization. For treatment-related adverse events, the χ^2 test (or Fisher's exact test if one or more cells had $n < 5$) was used to compare among the three groups for statistical significance.

RESULTS

OVER THE 3-MONTH PERIOD, THE MEAN IOP REDUCTION from baseline produced by travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution (Trav/Tim) was 1.9 mm Hg to 3.3 mm Hg more than the mean IOP reduction from baseline produced by timolol 0.5% ophthalmic solution (Tim) (Figure 1). Patients who received Trav/Tim showed a larger decrease in mean IOP compared with patients receiving Tim alone ($P \leq .003$) at each measurement time (8 AM, 10 AM, and 4 PM) during each on-therapy visit. Mean IOP for the Trav/Tim group was

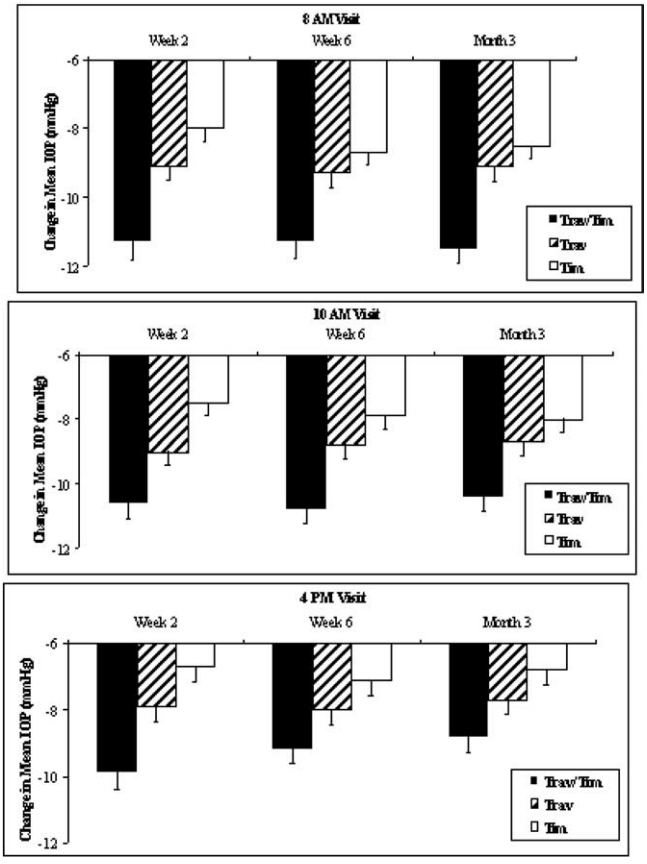

FIGURE 2. Change in mean IOP from Baseline (±SEM) at the 8:00 AM, 10:00 AM, and 4:00 PM IOP measurement time points (Refer to Table 3 for *P* values).

1.5 mm Hg to 2.7 mm Hg lower than mean IOP for the travoprost 0.004% ophthalmic solution (Trav) group. The reduction in IOP was numerically greater in the Trav/Tim group than in the Trav group at every time point and statistically significantly greater at seven of the nine time points ($P \leq .02$).

Two hundred and sixty-three patients were enrolled in the study. Of these, 258 completed at least one on-therapy visit and thus could be analyzed for efficacy of treatment. Eighty-two patients were assigned to the Trav/Tim group, 84 to the Trav group, and 92 to the Tim group. Of the 258 patients included in the analysis, all of them (100%) returned for the week 2 visit, 252 patients (98%) returned for the week 6 visit, and 248 patients (96%) returned for the month 3 visit. Patients ranged from age 31 to 91 years with a mean age (± SD) of 63.0 ± 11.2 years. There was no statistical difference among treatment groups ($P = .288$) for age. Furthermore, there were no statistically significant differences among treatment groups for gender, ethnicity, iris color, or diagnosis (Table 1).

Mean IOP is summarized in Table 2. Baseline IOPs, which were determined by the mean of the two eligibility visits, were similar at each time point among the three treatment groups ($P = .1503$). Each treatment group

TABLE 3. Mean IOP ± SD (mm Hg) Change from Baseline for Patients on Travoprost 0.004%/Timolol 0.5%, Travoprost 0.004%, or Timolol 0.5% Therapy

Visit	Trav/Tim (n = 82)	Trav (n = 84)	*P* Value*	Tim (n = 92)	*P* Value†
Week 2					
8 AM	−11.3 ± 4.7	−9.1 ± 3.8	<.001	−8.0 ± 3.3	<.001
10 AM	−10.6 ± 4.5	−9.0 ± 3.7	.018	−7.5 ± 3.4	<.001
4 PM	−9.9 ± 4.2	−7.9 ± 4.1	.004	−6.7 ± 3.9	<.001
Week 6					
8 AM	−11.3 ± 4.2	−9.3 ± 3.9	.001	−8.7 ± 3.1	<.001
10 AM	−10.8 ± 3.9	−8.8 ± 4.0	.002	−7.9 ± 3.5	<.001
4 PM	−9.2 ± 3.8	−8.0 ± 3.9	.077	−7.1 ± 4.0	.001
Month 3					
8 AM	−11.5 ± 3.9	−9.1 ± 4.3	<.001	−8.5 ± 3.5	<.001
10 AM	−10.4 ± 4.0	−8.7 ± 3.8	.008	−8.0 ± 3.8	<.001
4 PM	−8.8 ± 4.2	−7.7 ± 3.8	.122	−6.8 ± 4.1	.002

IOP = intraocular pressure; Tim = timolol 0.5%; Trav = travoprost 0.004%; Trav/Tim = Travoprost 0.004%/Timolol 0.5% fixed combination.

*Comparison of TravTim to Trav.

†Comparison of TravTim to Tim.

produced a significant reduction in mean IOP compared with baseline at all visits. Mean IOP was lowest in the Trav/Tim group with IOPs ranging from 17.3 mm Hg to 18.9 mm Hg. IOP ranged from 18.7 mm Hg to 20.5 mm Hg for the Trav group and 19.8 mm Hg to 21.3 mm Hg for the Tim group.

Change in mean IOP from baseline was greatest in the Trav/Tim group at the 8 AM, 10 AM, and 4 PM (Table 3) (Figure 2, top, middle, and bottom, respectively) visits. Over the 3-month treatment period Trav/Tim produced a significant decrease in IOP compared with baseline at the 8 AM time point at each on-therapy visit compared with either Trav ($P \leq .001$) or Tim ($P < .001$). At the 8 AM time point Trav/Tim decreased IOP by 2.0 to 2.4 mm Hg more than Trav. Furthermore, change in mean IOP was significantly greater with Trav/Tim at each 10 AM time point compared with either Trav ($P \leq .018$) or Tim ($P < .001$) over the 3-month treatment period. Trav/Tim produced a greater reduction of IOP at the 4 PM time point compared with Tim at all visits ($P \leq .002$) over the 3 months of treatment. The 4 PM change in mean IOP from baseline was significantly greater with Trav/Tim compared with Trav at the week 2 visit ($P = .004$), and was numerically superior at the week 6 ($P = .077$) and month 3 ($P = .122$) visits. Mean percent IOP reductions from baseline are shown in Table 4

All 263 patients enrolled in the study received study medication and were thus evaluable for safety analysis. The most frequently reported treatment-related adverse event in the Trav/Tim and Trav treatment groups was patient-reported ocular hyperemia occurring at an incidence of 14% and 12%, respectively. The most frequently reported treatment-related adverse event in the Tim treatment group was ocular discomfort occurring at an incidence of 7%. A list of treatment-related adverse events, both ocular and non-ocular, occurring at an incidence above 2% is provided in Table 5.

No clinically relevant, treatment-related changes in visual acuity, ocular signs (iris/anterior chamber, lens), dilated fundus parameters, cup/disk ratio, or visual fields were observed following exposure to study drug. No safety concerns were identified when analyzing ocular sign parameter changes from baseline following exposure to study drug. Clinically relevant, treatment-related changes in ocular signs (cornea, aqueous flare, inflammatory cells) following exposure to study drug were resolved with or without treatment, and did not interrupt continued patient participation in the study. No safety concerns were identified when analyzing ocular hyperemia results or iris/eyelash photographs. No safety concerns were noted based upon an assessment of cardiovascular parameters (pulse rate, systolic and diastolic blood pressure) with this analysis including a review of the ranges of change from baseline, mean changes from baseline, shift table analysis of changes from baseline, a review of scatter plot data, and review of individual patient data.

DISCUSSION

THE RESULTS OF THIS STUDY SHOW THAT TRAVOPROST 0.004%/timolol 0.5% fixed combination ophthalmic solution (Trav/Tim) dosed once daily in the morning is superior in reducing mean IOP compared with single-agent therapy with either travoprost 0.004% ophthalmic solution (Trav) dosed once daily in the evening or timolol 0.5% ophthalmic solution (Tim) dosed twice daily (morning and evening). Trav/Tim produced reductions in mean

TABLE 4. Mean Percentage IOP Reduction From Baseline for Patients on Travoprost 0.004%/Timolol 0.5%, Travoprost 0.004%, or Timolol 0.5% Therapy

Visit	Trav/Tim (n = 82) %	Trav (n = 84) %	Tim (n = 92) %
Week 2			
8 AM	−37	−31	−27
10 AM	−37	−32	−27
4 PM	−36	−29	−25
Week 6			
8 AM	−37	−31	−30
10 AM	−38	−31	−28
4 PM	−33	−30	−26
Month 3			
8 AM	−38	−31	−29
10 AM	−36	−31	−29
4 PM	−32	−29	−25

IOP = intraocular pressure; Tim = timolol 0.5%; Trav = travoprost 0.004%; Trav/Tim = Travoprost 0.004%/Timolol 0.5% Fixed Combination.

TABLE 5. Treatment-Related Adverse Events Occurring at an Incidence Greater Than 2% for Patients on Travoprost 0.004%/Timolol 0.5%, Travoprost 0.004%, or Timolol 0.5% Therapy

	Trav/Tim n = 85		Trav n = 86		Tim n = 92	
	n	%	n	%	n	%
Ocular						
Hyperemia	12	14.1	10	11.6	1	1.1
Discomfort	6	7.1	2	2.3	6	6.5
Pruritus	2	2.4	2	2.3	1	1.1
Dry eye	2	2.4	2	2.3	2	2.2
Photophobia	4	4.7	1	1.2	0	0
Foreign body sensation	2	2.4	2	2.3	1	1.1
Hair disorder	4	4.7	1	1.2	0	0
Keratitis	2	2.4	1	1.2	0	0
Blurred vision	1	1.2	0	0	2	2.2
Lid disorder	1	1.2	2	2.3	0	0
Pain	0	0	3	3.5	0	0
Non-ocular						
Headache	2	2.4		0	1	1.1

Tim = timolol 0.5%; Trav = travoprost 0.004%; Trav/Tim = Travoprost 0.004%/Timolol 0.5% fixed combination.

IOP of approximately 9 to 12 mm Hg from baseline over 3 months of treatment. This change in mean IOP produced by Trav/Tim was superior compared with Tim at all time points and superior to Trav at seven of nine time points, including all the diurnal peak 8 AM IOP assessments. The safety of Trav/Tim was similar to Trav and was not associated with any severe or serious treatment-related adverse events.

Reduction of IOP has historically been the primary goal of glaucoma treatment and has been the most established means to prevent the progression of visual field loss and ganglion cell death.[16] However, until recently, large-scale, long-term studies on specific treatment parameters have been unavailable, including target IOP levels for treatment, acceptable amounts of diurnal IOP fluctuation, and a consensus on what baseline IOP value would lead to eventual glaucomatous damage. Clinicians are now armed with the results of several large multicenter clinical trials (Advanced Glaucoma Intervention Study [AGIS], the Collaborative Initial Glaucoma Treatment Study [CIGTS], the Ocular Hypertension Treatment Study [OHTS], the Early Manifest Glaucoma Trial [EMGT]) which address these parameters, confirming the benefit of IOP reduction in slowing the progression of, or even preventing, glaucomatous visual field, and optic nerve changes.[2,11,17,18] While the target goal varied from study to study, one significant consensus is an indication that reduction of IOP to 21 mm Hg, a previously common target IOP for therapy, is not adequate for many patients.

The AGIS addressed the importance of maintaining low IOP to prevent visual field deterioration.[2] In this study, patients whose IOPs were maintained below 18 mm Hg had the least visual field degeneration over the 8 years of the study. Therefore, a treatment regimen that can maintain IOP lower than 18 mm Hg would be expected to prevent or significantly slow the progression of visual field loss in glaucoma patients. However, maintaining IOP levels less than 18 mm Hg may not be achieved with a single medication in many patients.

The reduction in IOP produced by Trav/Tim was more pronounced at the 8 AM time point, the peak of the diurnal IOP curve. Previous studies have shown that diurnal IOP fluctuations lead to an increased risk for progression of visual field loss.[19] Moreover, IOP is generally highest in the morning in the majority of glaucoma patients.[10,20] This study showed that Trav/Tim had its greatest impact at the 8 AM IOP assessment (Figure 2, top), with reductions in mean IOP change from baseline of approximately 12 mm Hg (38%) over the 3 months of treatment, compared with an approximately 9 mm Hg reduction with Trav.

When choosing a treatment for a glaucoma patient, compliance is an important consideration. Research has shown that fewer medications and simpler dosing schedules increase patient compliance.[12–16,21] Combination products offer an obvious advantage in this regard. For example, the introduction of dorzolamide hydrochloride-timolol maleate ophthalmic solution (COSOPT, Merck & Co., Inc., Whitehouse Station, New Jersey) was based on IOP-lowering efficacy that was numerically less but statistically non-inferior to the concomitant use of the two medications dosed separately.[22] Indeed, in a subsequent study more closely approximating clinical

practice, dorzolamide hydrochloride-timolol maleate ophthalmic solution demonstrated enhanced efficacy over its component medications dosed separately, highlighting the possibility of increased patient compliance.[23] The use of a fixed combination product should reduce the exposure to ophthalmic preservatives compared with the concomitant administration of multiple drops. Furthermore, a fixed combination can reduce the cost to patients compared with multiple prescriptions.

The results of this study show that over the course of the 3 months of treatment, Trav/Tim dosed once daily in the morning is more effective in reducing IOP than either Trav dosed once daily in the evening or Tim dosed twice daily. Additionally, Trav/Tim was safe and well tolerated with an incidence of adverse events comparable to Trav or Tim alone.

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Biosketch

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