Travoprost Compared With Latanoprost and Timolol in Patients With Open-angle Glaucoma or Ocular Hypertension

PETER A. NETLAND, MD, PHD, THERESA LANDRY, PHD, E. KENNETH SULLIVAN, PHD, RUSSELL ANDREW, MS, LEWIS SILVER, PHD, ALAN WEINER, PHD, SUSHANTA MALLICK, PHD, JAIME DICKERSON, PHD, M. V. W. BERGAMINI, PHD, S. M. ROBERTSON, PHD, ALBERTA A. DAVIS, PHD, AND THE TRAVOPROST STUDY GROUP

• PURPOSE: This study evaluated the safety and intraocular pressure–lowering efficacy of two concentrations of travoprost (0.0015% and 0.004%) compared with latanoprost 0.005% and timolol 0.5% in patients with open-angle glaucoma or ocular hypertension.

• METHODS: Eight hundred one patients with open-angle glaucoma or ocular hypertension were randomly assigned to travoprost 0.0015%, travoprost 0.004%, latanoprost 0.005%, or timolol 0.5%. The efficacy and safety of travoprost (0.0015% and 0.004%) daily was compared with latanoprost daily and timolol twice daily for a period of 12 months.

• RESULTS: Travoprost was equal or superior to latanoprost and superior to timolol with mean intraocular pressure over visits and time of day ranging from 17.9 to 19.1 mm Hg (travoprost 0.0015%), 17.7 to 19.1 mm Hg (travoprost 0.004%), 18.5 to 19.2 mm Hg (latanoprost), and 19.4 to 20.3 mm Hg (timolol). For all visits pooled, the mean intraocular pressure at 4 PM for travoprost was 0.7 mm Hg (0.0015%, $P = .0502$) and 0.8 mm Hg (0.004%, $P = .0191$) lower than for latanoprost. Travoprost 0.004% was more effective than latanoprost and timolol in reducing intraocular pressure in black patients by up to 2.4 mm Hg (versus latanoprost) and 4.6 mm Hg (versus timolol). Based on a criterion of 30% or greater intraocular pressure reduction from diurnal baseline or intraocular pressure 17 mm Hg or less, travoprost 0.0015% and 0.004% had an overall response to treatment of 49.3% and 54.7%, respectively, compared with 49.6% for latanoprost and 39.0% for timolol. Iris pigmentation change was observed in 10 of 201 of patients (5.0%) receiving travoprost 0.0015%, six of 196 of patients (3.1%) receiving travoprost 0.004%, 10 of 194 of patients (5.2%) receiving latanoprost, and none of the patients receiving timolol (0 of 196). The average ocular hyperemia score was less than 1 on a scale of 0 to 3, indicating that on average patients experienced between none/trace and mild for all treatment groups. There were no serious, unexpected, related adverse events reported for any therapy.

• CONCLUSIONS: Travoprost (0.0015% and 0.004%), a highly selective, potent prostaglandin F (FP) receptor agonist, is equal or superior to latanoprost and superior to timolol in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. In addition, travoprost 0.004% is significantly better than either latanoprost or timolol in lowering intraocular pressure in black patients. Travoprost is safe and generally well tolerated in the studied patient population. (Am J Ophthalmol 2001;132:472–484. © 2001 by Elsevier Science Inc. All rights reserved.)

Accepted for publication Jul 17, 2001.

From the University of Tennessee Health Science Center (P.A.N.), Memphis, Tennessee, and Alcon Research, Ltd (T.L., E.K.S., R.A., L.S., A.W., S.M., J.D., M.V.W.B., S.M.R., A.A.D.), Fort Worth, Texas..

This study was presented in part at the Annual Meeting of the American Glaucoma Society, Newport Beach, California, March 2, 2001, and at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, May 2, 2001.

This study was supported by Alcon Research, Ltd. Dr Netland was a clinical investigator for this study and has no proprietary interest in travoprost or any other product in this manuscript. Proprietary rights for travoprost are retained by Alcon Research, Ltd, 6201 S. Freeway, Fort Worth, Texas 76134.

Reprint requests to Peter A. Netland, MD, PhD, Department of Ophthalmology, University of Tennessee Health Science Center, 956 Court Ave, Memphis, TN 38163; fax: (901) 448-1299; e-mail: pnetland@mail.eye.utmem.edu

ELEVATED INTRAOCULAR PRESSURE IS A RISK FACTOR that contributes to optic nerve damage and subsequent visual field loss in patients with glaucoma or ocular hypertension. Prostaglandin analogues represent a class of active ocular hypotensive agents that reduce intraocular pressure as effectively as nonselective β-adren-

0002-9394/01/$20.00
PII S0002-9394(01)01177-1

ergic antagonists, frequently the standard treatment used in glaucoma therapy, without the unwanted systemic side effects associated with this class of compounds. The reduction of intraocular pressure by analogues of $PGF_{2\alpha}$ is largely the result of increased uveoscleral outflow of aqueous humor.[1,2]

Travoprost is a topical ocular isopropyl ester prodrug that is rapidly hydrolyzed by esterases in the cornea to the biologically active, free acid that is structurally similar to fluprostenol and other prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogues. Travoprost acid has greater affinity for the prostaglandin F (FP) receptor than either $PGF_{2\alpha}$ or latanoprost acid with a Ki of 52 nM versus 129 nM for $PGF_{2\alpha}$ and 92 nM for latanoprost acid in bovine corpus luteum binding studies. It has demonstrated preferential affinity and full agonist activity for the FP receptor in the nanomolar range with no meaningful affinity or activity on other receptors.[3–5]

The intraocular pressure–lowering activity of travoprost has been evaluated in the laser-induced ocular hypertensive monkey model.[5] In this model, dose-related intraocular pressure reductions of 17% to 30% were obtained after twice daily dosing of 0.00033% to 0.001% concentrations (0.1 and 0.3 μg doses) of travoprost. Once daily dosing with 0.001% (0.3 μg) resulted in 22% and 30% reductions of intraocular pressure observed 16 to 24 hours after dosing. Once-daily administration with 0.0033% (1 μg) provided intraocular pressure–lowering efficacy equivalent to the 0.001% dose (unpublished data). Based on these data and the efficacy and safety results from two dose–response studies by Alcon Laboratories, the top of the dose–response curve was determined to be 0.004%.[6] This dose and an intermediate dose of 0.0015% were selected for further development and study. The earlier dose–response studies also confirmed no difference in response to AM versus PM dosing, and therefore PM dosing was selected on the basis of patient convenience and hyperemia considerations.

This multicenter, randomized, double-masked, clinical study compared the efficacy and safety of travoprost ophthalmic solution (0.0015% and 0.004%), applied once daily in the evening, with latanoprost 0.005%, applied once daily in the evening, and timolol 0.5%, applied twice daily in the morning and evening, in patients with open-angle glaucoma or ocular hypertension for a period of 1 year.

PATIENTS AND METHODS

THIS WAS A RANDOMIZED, MULTICENTER, DOUBLE-masked, active-controlled, parallel group study conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. Eight hundred one patients were randomized to one of four treatment groups in an approximate 1:1:1:1 ratio, (travoprost 0.0015%, n = 205; travoprost 0.004%, n = 200; timolol, n = 200; latanoprost, n = 196). The Alcon Biostatistics Department prepared the computer-generated randomization schedule. All patients were included in the safety analysis. An institutional review board approved this study, and all patients or their legal representative read, signed, and dated an institutional review board–approved consent form before participating in the study.

Patients who were enrolled were of either sex and any race diagnosed with either open-angle glaucoma (with or without pseudoexfoliative or pigmentary glaucoma) or ocular hypertension. They were required to have intraocular pressure measurements of 24 to 36 mm Hg, inclusive, in the same eye(s), at the 8 AM intraocular pressure measurements, at two eligibility visits, at least 7 days apart. Although both eyes could have met these criteria, only one eye was required to meet these criteria for patient eligibility. Additionally, intraocular pressure measurements must have been 21 to 36 mm Hg, inclusive, in the same eye(s), at the 10 AM and 4 PM examinations at both eligibility visits, and intraocular pressure in both eyes must have been less than or equal to 36 mm Hg at all times. Contact lens wear was not allowed during this study. Patients who met the inclusion criteria at the screening visit and were taking glaucoma medication(s) underwent a washout period (in which all glaucoma medications were discontinued) of 3 weeks for β antagonists and prostaglandins, 2 weeks for α and α/β agonists, 5 days for miotics, 5 days for oral or topical carbonic anhydrase inhibitors, and 3 days if no ocular hypotensive medications were being used.

Exclusion criteria were chosen primarily for safety concerns and to further characterize the study population. Women who were of childbearing potential were excluded and all women who entered into the study must have been either postmenopausal for 1 year or surgically sterilized at least 3 months before the start of the study. Patients with intraocular pressure greater than 36 mm Hg in either eye during the eligibility phase were excluded on the basis of potential safety risk during this long-term study, as were patients with best-corrected visual acuity worse than 0.60 logarithm of minimal angle of resolution (logMAR) in either eye. Other reasons for exclusion included chronic or recurrent severe inflammatory eye disease; a history of ocular trauma within the past 6 months; a history of ocular infection or ocular inflammation within the past 3 months; a history of progressive retinal disease or a history of severe ocular pathology in either eye that would preclude the administration of a topical β blocker or prostaglandin; a cup-to-disk ratio greater than 0.80 in either eye; intraocular surgery within the past 6 months; a history of severe or serious hypersensitivity to prostaglandins or systemic β blockers; a history of severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease, bronchial asthma, or severe chronic obstructive pulmonary disease that would preclude the safe administration of a topical β blocker. In addition, patients were excluded for use of any glucocor-

ticoid during the eligibility phase or use of topical, ocular nonsteroidal anti-inflammatory agents, which inhibit cyclooxygenase and prostaglandin synthesis, during the course of the study. Chronic glucocorticoid therapy was discontinued for at least 4 weeks and intermittent glucocorticoid use was discontinued for at least 2 weeks before the first eligibility visit. Patients who used any adjunctive therapy, either topical or systemic, for lowering intraocular pressure or who had therapy with another investigational agent within 30 days before randomization were also excluded.

The study visits included diurnal time points to allow frequent safety and efficacy monitoring and included two eligibility visits for baseline data and on-therapy planned visits at week 2, and at months 1.5, 3, 4.5, 6, 9, and 12. Examinations were performed at 8 AM, 10 AM, and 4 PM for the eligibility 1 and 2 visits and at week 2 and months 3, 6, and 12. Examinations were made at 8 AM and 10 AM at months 1.5, 4.5, and 9. Prerandomization baseline data included ocular and medical history; slit-lamp biomicroscopy examination; dilated fundus examination, including cup-to-disk ratio; gonioscopy, if not conducted within the last 6 months; visual field with automated perimetry for both eyes; visual acuity (logMAR scale); evaluation of ocular hyperemia, inflammatory cells, and aqueous flare; intraocular pressure measurement; iris and endothelial cell photography; resting pulse and blood pressure; and blood and urine samples.

Examinations for the study visits were performed as follows: week 2—intraocular pressure, hyperemia and flare/cells assessment, visual acuity, biomicroscopy and resting pulse and blood pressure; month 1.5, month 3, month 4.5—intraocular pressure, hyperemia and flare/cells assessment, visual acuity, biomicroscopy, resting pulse and blood pressure, and iris photography; month 6—intraocular pressure, hyperemia and flare/cells assessment, visual acuity, biomicroscopy, resting pulse and blood pressure, and iris photography; endothelial cell photography, pachymetry, resting pulse and blood pressure, and blood and urine samples; month 9—intraocular pressure, hyperemia and flare/cells assessment, visual acuity, biomicroscopy, resting pulse and blood pressure, and iris photography; month 12 (exit examination)—intraocular pressure, hyperemia and flare/cells assessment, visual acuity, biomicroscopy, resting pulse and blood pressure, dilated fundus, automated perimetry, iris and endothelial photography, pachymetry, and blood and urine samples. Endothelial cell density was measured at baseline, month 6, and month 12 or the exit examination at 8 AM. The mean change in endothelial cell density (cells/mm^2) of both eyes from baseline was calculated at month 6 and month 12.

Two different, trained individuals (a reader and an operator) determined intraocular pressure measurements with a recently calibrated Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland). Hyperemia assessment was made in ambient light, before intraocular pressure measurements and instillation of fluorescein, by the same masked observer throughout the study using a standard set of photographs depicting ocular hyperemia. The hyperemia scale was 0 = none/trace; 1 = mild; 2 = moderate; 3 = severe and could be reported in 0.5-U increments. A clinically significant change from baseline in ocular hyperemia was defined as an increase of one or more units from the maximum hyperemia score recorded at any of the prerandomization visits.

Photographs of each eye were taken to assess any change in iris pigmentation or eyelash characteristics. Iris color classifications were blue/gray, blue/gray with slightly brown, blue/gray-brown, green, green with slightly brown, green-brown, yellow-brown, and brown. Subsequent photographs were evaluated for any change from baseline by a group of ophthalmologists and scientists (masked) who had not examined the patients or were investigators in the study. All changes were confirmed at the last patient visit.

The visual field evaluation was performed with either a Humphrey Field Analyzer (Humphrey Instruments, Inc, San Leandro, California) program 24-2 or 30-2 equipped with STATPAC or FASTPAC or an Octopus perimeter (Interzeag AG, Schlierien, Switzerland) program G1 or G1X. SmithKline Beecham Clinical Laboratories Clinical Trials Center analyzed all laboratory specimens (blood chemistry, hematology, and urinalysis) with each site receiving common training on collecting, processing, and shipping of specimens. Laboratory reports were evaluated, and out-of-range values were assessed.

An adverse event was any change from baseline in the ophthalmic or medical health of the patient during the study. These events were obtained as investigator observations or solicited complaints from the patient at each visit, and patients were discontinued from the study if the investigator considered the patient at risk or if the patient chose to discontinue for any reason.

To maintain masking, all patients received two identical DROPTAINER bottles labeled with a patient number and "morning" or "evening" according to the computer-generated randomization schedule provided by the Biostatistics Department at Alcon Laboratories. For patients randomized to timolol, both bottles contained active medication, whereas patients who received travoprost (0.0015% and 0.004%) or latanoprost received active medication in the bottle labeled "evening" and travoprost vehicle (placebo) in the bottle labeled "morning." The active test medication and vehicle were indistinguishable from each other, because the vehicle formulation contained the same ingredients as the active formulation devoid of the active component. Test article and vehicle contained benzalkonium chloride 0.015% as the preservative. Patients were instructed to instill one drop in each eye at 8 AM from the bottle labeled "morning" and at 8 PM from the bottle labeled "evening" except on the mornings of study visits. On study visits, patients were dosed in the office after the 8 AM intraocular pressure measurement. Sealed envelopes

containing the description of the medication for each patient were provided to the investigator. The treatment code was broken for one patient who complained of breathing difficulty. The principal investigator, patient, and sponsor remained unaware of the identity of the study medication, and the patient continued to participate in the study under the supervision of different site personnel to maintain masking.

All statistical analyses were conducted as set forth in the signed and archived Biostatistics Analysis Plan for this study. The analysis plan was reviewed before database lock and breaking the mask for randomized treatment assignment to ensure compliance with the principles for statistical analysis of clinical trials established by the International Conference on Harmonization.[7] Clarifications to the plan were made at the time of review to address recent understanding of regulatory interpretation for this study,[8] but the primary efficacy and safety analyses developed in the original analysis plan remained unchanged.

A mixed-effects repeated measures analysis of variance model was used in the analysis of the efficacy parameter to make treatment group comparisons and to estimate confidence limits. Treatment group, visit day, and visit time of day were analyzed as fixed effects, and patient nested within treatment group was analyzed as a random effect to take into account the repeated measurements on a patient. Unless otherwise noted, all estimates presented in this report are based on least squares means from the repeated measures analysis of variance. All tests were conducted with a 5% chance of an experiment-wise type 1 error, controlling for multiple comparisons using a sequential testing procedure.[9] Analysis of the safety parameters was conducted using analysis of variance models, Mantel-Haenszel chi-square tests, Pearson chi-square tests, or Fisher's exact tests, as appropriate, depending on the variable being analyzed. All analyses were performed using SAS for Windows, version 6.12 (SAS Institute, Inc, Cary, North Carolina).

Three analysis data sets—safety, intent-to-treat, and per protocol—were used. The safety data set included all patients who received study medication; the intent-to-treat data set included all patients who received study medication and completed at least one on-therapy scheduled visit; and the per protocol data set included all patients who received study medication, completed at least one on-therapy scheduled visit, and satisfied protocol inclusion/exclusion criteria. In addition, only those data points that satisfied protocol criteria were included in the per protocol data set. The findings in this report are primarily based on the intent-to-treat data because of the similarity of results from the intent-to-treat and per protocol analyses.

The sample size was chosen based on a greater than 90% probability that with 150 patients per group a 95% two-sided confidence interval would fall within ± 1.5 mm Hg for a test of noninferiority. For a test of superiority, there was more than 90% power to detect a difference of 1.5 mm Hg between treatments. The sample sizes were based on a standard deviation for intraocular pressure of 3.5 mm Hg and a two-sample *t* test conducted at a 5% chance of a type 1 error.

The primary efficacy parameter was mean intraocular pressure at 8 AM, 10 AM and 4 PM for the patient's worse eye defined as follows:

- The eye with the higher intraocular pressure at 8 AM averaged across both eligibility visits. If both eyes were equal then,
- The eye with the higher intraocular pressure at 10 AM averaged across both eligibility visits. If both eyes were equal then,
- The eye with the higher intraocular pressure at 4 PM averaged across both eligibility visits. If both eyes were equal then, the right eye was selected for analysis.

The primary objectives for this study were to show that travoprost (0.0015%, 0.004%) was greater than or equal to timolol intraocular pressure–lowering efficacy; travoprost 0.004% was greater than or equal to latanoprost in intraocular pressure–lowering efficacy; and to determine whether travoprost 0.004% was superior to travoprost 0.0015% in intraocular pressure–lowering efficacy. The analyses of demographic comparisons, mean intraocular pressure by race, age, gender, iris color, and diagnosis were prospectively planned in the biostatistics analysis plan. The study was conducted as originally planned with no amendments to the protocol.

RESULTS

EIGHT HUNDRED ONE PATIENTS WERE RANDOMIZED TO one of four treatments. All 801 patients were included in the safety analysis. Fourteen patients were excluded from the intent-to-treat analysis because of no on-treatment visit data (travoprost 0.0015% − N = 3; travoprost 0.004% − N = 3; latanoprost − N = 3; timolol − N = 5) resulting in 787 patients in the intent-to-treat data set. Forty-one patients were excluded from the per protocol analysis (travoprost 0.005% − N = 7; travoprost 0.004% − N = 13; latanoprost − N = 8; timolol − N = 13) because of protocol violations. These violations included nonqualifying intraocular pressure, inadequate time interval from dosing to intraocular pressure measurement, contraindicated concomitant medication, and improper dosing of or noncompliance to study medication, resulting in 760 patients in the per protocol data set.

The mean ± standard deviation age (and age ranges) for the travoprost 0.0015%, travoprost 0.004%, timolol 0.5%, and latanoprost 0.005% groups was 63.7 ± 11.0 (35 to 88 years), 64.0 ± 13.3 (22 to 94 years), 64.8 ± 11.6 (25 to 87 years), and 64.5 ± 11.6 (28 to 86 years) years old, respectively. Analysis of variance showed no significant

TABLE 1. Demographic Comparisons

	Travoprost 0.0015%		Travoprost 0.004%		Timolol 0.5%		Latanoprost 0.005%		*P*
	n	%	*n*	%	*n*	%	*n*	%	Value*
Age									
<65 years	103	51.0	86	43.7	75	38.5	86	44.6	.094
≥65 years	99	49.0	111	56.3	120	61.5	107	55.4	
Age (≥ 65 years)									
≥65 to <75 years	63	63.6	72	64.9	84	70.0	62	57.9	
≥75 to <85 years	33	33.3	36	32.4	33	27.5	44	41.1	.460
≥85 to <95 years	3	3.0	3	2.7	3	2.5	1	0.9	
Sex									
Male	96	47.5	100	50.5	107	54.9	89	46.1	.315
Female	106	52.5	97	49.2	88	45.1	104	53.9	
Race									
Caucasian	147	72.8	138	70.1	146	74.9	135	69.9	
Black	45	22.3	49	24.9	40	20.5	43	22.3	.807
Asian	2	1.0	2	1.0	0	0	2	1.0	
Other	8	4.0	8	4.1	9	4.6	13	6.7	
Iris color†									
Brown	108	53.5	106	53.8	90	46.2	114	59.1	
Hazel	27	13.4	23	11.7	28	14.4	24	12.4	.395
Green	8	4.0	10	5.1	11	5.6	8	4.1	
Blue	56	27.7	52	26.4	59	30.3	38	19.7	
Grey	3	1.5	5	2.5	7	3.6	9	4.7	
Diagnosis									
Ocular hypertension	66	32.7	67	34.0	55	28.2	59	30.6	
Open-angle glaucoma	134	66.3	127	64.5	137	70.3	132	68.4	.632
Pigmentary glaucoma	0	0	3	1.5	2	1.0	1	0.5	
Pseudoexfoliation glaucoma	2	1.0	0	0	1	0.5	1	0.5	

**P* values from chi-square test of independence.
†Iris color not obtained for one patient (0.5%) in the travoprost 0.004% group.

difference in the mean age among groups ($P = .7855$). Other demographic comparisons are shown in Table 1. There were no statistically significant differences between treatment groups for age distribution (elderly versus non-elderly, $P = .094$), sex ($P = .315$), race ($P = .807$), iris color ($P = .395$), or ocular diagnosis ($P = .632$).

The intraocular pressure–lowering efficacy of travoprost (0.0015% and 0.004%) dosed once daily in the evening was equal or superior to that of latanoprost dosed once daily in the evening at all treatment visits with mean intraocular pressure ranging from 17.7 to 19.5 mm Hg (travoprost 0.0015%), 17.5 to 19.7 mm Hg (travoprost 0.004%), and 17.9 to 19.5 mm Hg (latanoprost) (Table 2). The mean intraocular pressure was significantly lower for travoprost compared with latanoprost at the week 2 visit and was statistically equivalent at the other visits in the study.

The intraocular pressure reductions from baseline produced by travoprost (0.0015% and 0.004%) were statistically significant at all measurement times. Mean intraocular pressure reductions ranged from −6.0 to −7.7 mm Hg for the travoprost 0.0015% and from −6.6 to −8.1 mm Hg for the travoprost 0.004% concentration. Mean intraocular pressure reductions ranged from −6.2 to −8.1 mm Hg for latanoprost and from −4.7 to −7.1 mm Hg for timolol. Mean baseline values (mm Hg) for intraocular pressure, pooled across visit times, were 25.1 (0.0015%), 25.5 (0.004%), 25.7 (timolol), and 25.7 (latanoprost) with no significant difference between groups.

The intraocular pressure–lowering efficacy of travoprost (0.0015% and 0.004%) in all patients was significantly greater at all visits and time points compared with timolol, with mean intraocular pressure ranging from 17.5 to 19.7 mm Hg for travoprost (0.0015% and 0.004%) and 19.1 to 20.7 mm Hg for timolol (Figure 1). Mean intraocular pressure reductions ranged from −6.0 to −8.1 mm Hg for travoprost (0.0015% and 0.004%) compared with timolol, which ranged from −4.7 to −7.1 mm Hg. When the two concentrations of travoprost were compared, mean intraocular pressure in the travoprost 0.004% group was lower than in the 0.0015% group at 13 of 18 treatment visits by up to 0.5 mm Hg in favor of the 0.004%

TABLE 2. Mean Intraocular Pressure Comparisons Among Treatment Groups

	Baseline			Pooled			Week 2			Month 1.5		Month 3			Month 4.5		Month 6			Month 9		Month 12		
Treatment	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM
Travoprost 0.004%	26.8	25.1	24.5	19.1	17.8	17.7	18.9	17.6	17.5	18.9	17.5	18.8	17.8	17.8	19.0	17.9	19.2	17.8	18.0	19.3	18.2	19.7	18.2	17.9
Latanoprost 0.005%	26.9	25.2	24.9	19.2	18.2	18.5	19.5	18.5	18.7	18.8	18.2	19.1	18.1	18.2	18.9	18.0	19.2	17.9	18.4	19.5	18.3	19.4	18.1	18.6
Difference	−0.0	−0.1	−0.4	−0.1	−0.3	−0.8	−0.6	−0.9	−1.2	0.1	−0.7	−0.3	−0.3	−0.5	0.1	−0.1	−0.0	−0.1	−0.4	−0.2	−0.1	0.4	0.1	−0.6
P value	0.8977	0.8047	0.1788	0.7899	0.2885	0.0191	0.1147	0.0162	0.0012	0.7759	0.0735	0.3742	0.4347	0.2061	0.7694	0.7119	0.9567	0.7072	0.2986	0.6264	0.7198	0.3441	0.8637	0.1050
Travoprost 0.0015%	26.4	24.8	24.1	19.1	18.0	17.9	19.2	18.0	17.9	18.9	17.8	18.7	17.9	17.7	19.0	18.1	19.2	17.8	17.9	19.5	18.3	19.4	18.3	18.1
Latanoprost 0.005%	26.9	25.2	24.9	19.2	18.2	18.5	19.5	18.5	18.7	18.8	18.2	19.1	18.1	18.2	18.9	18.0	19.2	17.9	18.4	19.5	18.3	19.4	18.1	18.6
Difference	−0.5	−0.4	−0.8	−0.1	−0.1	−0.7	−0.3	−0.4	−0.8	0.2	−0.3	−0.4	−0.3	−0.6	0.2	0.1	−0.1	−0.1	−0.4	0.0	−0.0	0.1	0.2	−0.5
P value	0.0923	0.1840	0.0050	0.8603	0.6975	0.0502	0.4508	0.2343	0.0395	0.6588	0.3542	0.2469	0.4876	0.1210	0.6572	0.8453	0.7974	0.8711	0.2443	0.9368	0.9668	0.8223	0.5119	0.2050
Travoprost 0.004%	26.8	25.1	24.5	19.1	17.8	17.7	18.9	17.6	17.5	18.9	17.5	18.8	17.8	17.8	19.0	17.9	19.2	17.8	18.0	19.3	18.2	19.7	18.2	17.9
Timolol 0.5%	27.0	25.4	24.6	20.3	19.4	19.4	20.0	19.3	19.2	19.9	19.1	20.1	19.3	19.3	20.1	19.2	20.3	19.6	19.5	20.6	19.8	20.7	19.9	19.9
Difference	−0.2	−0.3	−0.1	−1.2	−1.6	−1.7	−1.1	−1.7	−1.7	−1.1	−1.6	−1.4	−1.5	−1.5	−1.1	−1.3	−1.1	−1.8	−1.5	−1.4	−1.6	−1.0	−1.7	−1.9
P value	0.5498	0.2993	0.8255	0.0001	0.0001	0.0001	0.0037	0.0001	0.0001	0.0040	0.0001	0.0003	0.0001	0.0001	0.0022	0.0007	0.0026	0.0001	0.0001	0.0002	0.0001	0.0091	0.0001	0.0001
Travoprost 0.0015%	26.4	24.8	24.1	19.1	18.0	17.9	19.2	18.0	17.9	18.9	17.8	18.7	17.9	17.7	19.0	18.1	19.2	17.8	17.9	19.5	18.3	19.4	18.3	18.1
Timolol 0.5%	27.0	25.4	24.6	20.3	19.4	19.4	20.0	19.3	19.2	19.9	19.1	20.1	19.3	19.3	20.1	19.2	20.3	19.6	19.5	20.6	19.8	20.7	19.9	19.9
Difference	−0.6	−0.6	−0.5	−1.1	−1.4	−1.5	−0.8	−1.3	−1.2	−1.0	−1.2	−1.5	−1.4	−1.6	−1.1	−1.1	−1.2	−1.8	−1.5	−1.2	−1.4	−1.2	−1.5	−1.8
P value	0.0308	0.0335	0.0930	0.0001	0.0001	0.0001	0.0370	0.0006	0.0010	0.0062	0.0009	0.0001	0.0001	0.0001	0.0034	0.0044	0.0012	0.0001	0.0001	0.0018	0.0001	0.0008	0.0001	0.0001
Travoprost 0.0015%	26.4	24.8	24.1	19.1	18.0	17.9	19.2	18.0	17.9	18.9	17.8	18.7	17.9	17.7	19.0	18.1	19.2	17.8	17.9	19.5	18.3	19.4	18.3	18.1
Travoprost 0.004%	26.8	25.1	24.5	19.1	17.8	17.7	18.9	17.6	17.5	18.9	17.5	18.8	17.8	17.8	19.0	17.9	19.2	17.8	18.0	19.3	18.2	19.7	18.2	17.9
Difference	−0.5	−0.3	−0.4	0.0	0.2	0.1	0.3	0.5	0.4	0.1	0.3	−0.1	0.0	−0.1	0.1	0.2	−0.1	0.1	−0.0	0.2	0.1	−0.3	0.2	0.1
P value	0.1182	0.2777	0.1437	0.9262	0.4946	0.6884	0.4024	0.2164	0.2298	0.8760	0.3794	0.7908	0.9264	0.7794	0.8811	0.5688	0.8391	0.8283	0.9053	0.5673	0.7482	0.4646	0.6272	0.7147

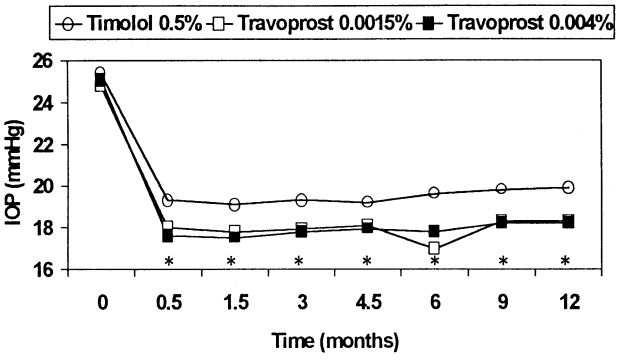

FIGURE 1. Mean intraocular pressure at 10:00 AM after administration of travoprost 0.0015%, travoprost 0.004%, and timolol 0.5%. The intraocular pressure was significantly lower after travoprost compared with timolol at each visit and at all time points. IOP = intraocular pressure; asterisks indicate statistically significant differences between the timolol and travoprost groups.

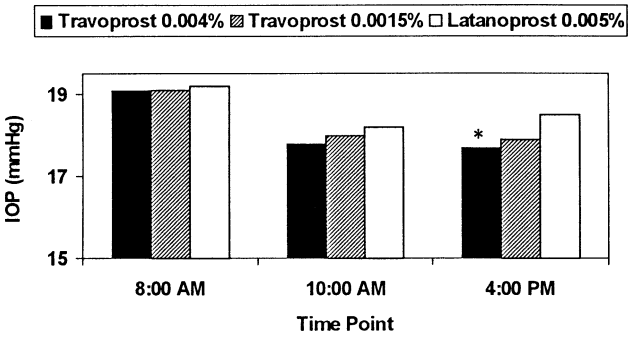

FIGURE 2. Mean intraocular pressure following travoprost 0.0015%, travoprost 0.004%, and latanoprost 0.005% at different time points (8:00 AM, 10:00 AM, and 4:00 PM), pooled from all visits. The baseline values were not significantly different for the travoprost 0.004% and the latanoprost 0.005% groups. The asterisk indicates that the mean intraocular pressure was significantly lower at the 4:00 PM time point for travoprost 0.004% compared with latanoprost 0.005% (P = .0191). IOP = intraocular pressure.

concentration. However, the difference between the two concentrations was not statistically significant (Table 2).

Mean intraocular pressure results at 8 AM, 10 AM, and 4 PM, pooled over treatment visits, indicate that the intraocular pressure–lowering efficacy of travoprost (0.004%) was enhanced over the day from 8 AM to 4 PM and was significantly better compared with latanoprost at 4 PM (Figure 2). At 4 PM, mean intraocular pressure for travoprost was 0.7 mm Hg (0.0015%, $P = .0502$) and 0.8 mm Hg (0.004%, $P = .0191$) lower than for latanoprost (Table 2). The mean intraocular pressure was lower for travoprost compared with latanoprost at four of five visits over the first 1.5 months of therapy. These differences were up to 1.2 mm Hg (0.004% versus latanoprost) and 0.8 mm Hg (0.0015% versus latanoprost) in favor of travoprost and were statistically significant ($P \leq .0162$) at two of the time points (0.004% versus latanoprost).

Black patients had lower mean intraocular pressure after treatment with travoprost 0.004% (16.7 to 18.4 mm Hg) compared with latanoprost (18.0 to 19.7 mm Hg) when results were pooled over treatment visits at the 8 AM, 10 AM, and 4 PM time points. This difference of up to 1.5 mm Hg was statistically significant ($P = .0356$) in favor of travoprost 0.004% (Table 3). Black patients also had a lower mean intraocular pressure after treatment with travoprost 0.004% compared with travoprost 0.0015% by up to 1.7 mm Hg in the pooled results. This 1.7 mm Hg difference was statistically significant ($P = .0064$) in favor of travoprost 0.004% (Figure 3).

Mean intraocular pressure for black patients in the travoprost groups (0.0015% and 0.004%) ranged from 16.2 to 19.9 mm Hg and 18.8 to 22.4 mm Hg in the timolol group with a difference of up to 4.6 mm Hg in favor of the travoprost 0.004% group, which was statistically significant ($P \leq .0028$; Figure 4). Mean intraocular pressure changes from baseline ranged from −6.9 to −8.9 mm Hg in the travoprost 0.004% group and −3.8 to −7.1 mm Hg in the timolol group. In contrast, mean intraocular pressure for nonblack patients ranged from 17.8 to 20.0 mm Hg in the travoprost 0.004% group and 19.0 to 20.3 mm Hg in the timolol group with a difference of 1.2 mm Hg in favor of travoprost 0.004%. Mean changes from baseline ranged from −6.3 to −7.8 mm Hg in the travoprost 0.004% group and −5.0 to −7.2 in mm Hg the timolol group (Table 4).

The percentage of patients who responded to treatment was based on a 30% or greater intraocular pressure reduction from diurnal baseline or a final intraocular pressure of 17 mm Hg or less. Travoprost 0.0015% and 0.004% groups had an overall response to treatment of 49.3% and 54.7%, respectively, compared with 49.6% for latanoprost and 39.0% for timolol (Figure 5). The differences between travoprost 0.004% and latanoprost ($P \leq .0430$) and timolol ($P \leq .0001$) were significant. Nonresponse to treatment was defined as a decrease of 3 mm Hg or less at 20 hours after dose. When data were pooled across visits and times, the nonresponder rates were 9% for travoprost 0.0015%, 8.6% for travoprost 0.004%, 22.5% for timolol, and 13.5% for latanoprost.

No serious, related adverse events were reported in this study, and adverse events that were reported were usually mild to moderate and resolved without treatment. The most frequent ocular adverse events (related and unrelated) included hyperemia, visual acuity decrease, pain, discomfort, and pruritus. Ocular and nonocular adverse events (combined related and unrelated) reported at an incidence of greater than 3% are identified in Table 5.

The percentages of patients with a clinically significant change from baseline in ocular hyperemia were 38.0% (78 of 205) for travoprost 0.0015%, 49.5% (99 of 200) for travoprost 0.004%, 27.6% (54 of 196) for latanoprost, and 14.0% (28 of

TABLE 3. Mean Intraocular Pressure Comparison of Travoprost (0.004% and 0.0015%) and Latanoprost 0.005%, by Race

	Baseline			Pooled			Week 2			Month 1.5		Month 3			Month 4.5		Month 6			Month 9		Month 12		
Treatment	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM
Black patients																								
Travoprost 0.004%	26.8	25.0	24.0	18.4	16.5	16.7	18.3	16.2	16.6	17.9	16.2	18.0	16.6	17.0	18.7	16.8	18.9	16.6	17.1	18.4	16.8	18.8	16.7	16.6
Latanoprost 0.005%	27.6	25.9	25.2	19.7	18.0	18.2	20.2	18.7	18.9	19.3	18.0	19.3	17.7	17.9	19.7	18.0	20.0	17.8	18.1	19.7	17.9	19.7	18.3	18.3
Difference	−0.8	−0.9	−1.2	−1.3	−1.5	−1.5	−1.9	−2.4	−2.2	−1.4	−1.9	−1.3	−1.1	−0.9	−1.0	−1.2	−1.1	−1.2	−1.0	−1.4	−1.0	−0.8	−1.6	−1.8
P value	0.1826	0.1604	0.0478	0.0354	0.0143	0.0356	0.0121	0.0016	0.0037	0.0626	0.0140	0.0798	0.1591	0.2491	0.1930	0.1311	0.1675	0.1126	0.1847	0.0725	0.1733	0.2762	0.0333	0.0219
Travoprost 0.0015%	26.1	25.0	24.3	19.4	18.2	17.5	19.8	18.1	18.2	19.4	17.9	18.0	17.5	17.4	19.3	18.1	19.7	18.2	17.9	19.9	18.6	19.4	18.8	17.8
Latanoprost 0.005%	27.6	25.9	25.2	19.7	18.0	18.2	20.2	18.7	18.9	19.3	18.0	19.3	17.7	17.9	19.7	18.0	20.0	17.8	18.1	19.7	17.9	19.7	18.3	18.3
Difference	−1.5	−0.8	−0.9	−0.3	0.1	−0.6	−0.4	−0.6	−0.7	0.1	−0.2	−1.3	−0.1	−0.5	−0.3	0.2	−0.3	0.5	−0.3	0.1	0.7	−0.2	0.5	−0.5
P value	0.0143	0.1809	0.1618	0.5960	0.8122	0.3804	0.5813	0.4551	0.3830	0.8793	0.8182	0.1079	0.8803	0.5553	0.6846	0.8182	0.6919	0.5421	0.7487	0.8756	0.3446	0.7698	0.5073	0.4830
Nonblack patients																								
Travoprost 0.004%	26.8	25.2	24.7	19.3	18.3	18.1	19.1	18.0	17.8	19.2	17.9	19.0	18.2	18.0	19.1	18.3	19.3	18.2	18.3	19.6	18.7	20.0	18.6	18.4
Latanoprost 0.005%	26.6	25.0	24.9	19.0	18.2	18.7	19.3	18.4	18.7	18.6	18.2	19.0	18.2	18.4	18.6	18.1	19.0	17.9	18.4	19.4	18.5	19.3	18.0	18.6
Difference	0.2	0.2	−0.1	0.3	0.1	−0.6	−0.2	−0.4	−0.9	0.6	−0.3	−0.0	−0.0	−0.3	0.4	0.2	0.3	0.2	−0.2	0.2	0.2	0.7	0.6	−0.2
P value	0.5829	0.6432	0.6758	0.3807	0.8129	0.1491	0.6748	0.3468	0.0393	0.1657	0.5394	0.9880	0.9809	0.4522	0.2996	0.6320	0.4935	0.6011	0.6894	0.6365	0.6566	0.0845	0.1478	0.6135
Travoprost 0.0015%	26.4	24.7	24.1	19.1	18.0	18.0	19.1	18.0	17.9	18.8	17.8	18.8	17.9	17.7	18.9	18.1	19.0	17.7	17.9	19.4	18.3	19.4	18.2	18.2
Latanoprost 0.005%	26.6	25.0	24.9	19.0	18.2	18.7	19.3	18.4	18.7	18.6	18.2	19.0	18.2	18.4	18.6	18.1	19.0	17.9	18.4	19.4	18.5	19.3	18.0	18.6
Difference	−0.2	−0.3	−0.8	0.0	−0.2	−0.7	−0.2	−0.4	−0.8	0.2	−0.4	−0.2	−0.3	−0.6	0.3	0.0	−0.0	−0.2	−0.5	0.0	−0.2	0.2	0.2	−0.4
P value	0.5504	0.4292	0.0150	0.9339	0.5681	0.0778	0.5727	0.3393	0.0603	0.6731	0.3509	0.6463	0.4774	0.1466	0.4696	0.9209	0.9360	0.6092	0.2480	0.9947	0.5799	0.6799	0.6947	0.2852

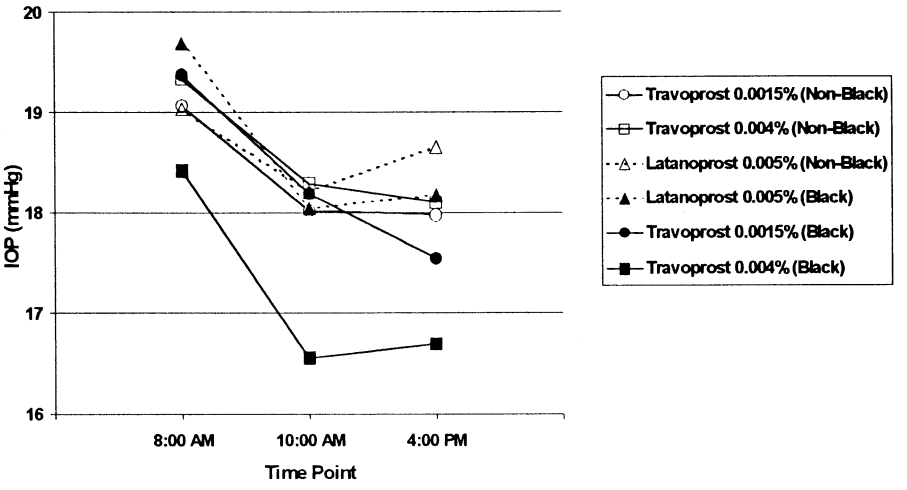

FIGURE 3. Mean intraocular pressure at different time points (pooled over all visits) for blacks and nonblacks after administration of travoprost and latanoprost. Travoprost 0.004% caused a significantly greater reduction of intraocular pressure in black patients compared with latanoprost (P = .0356). IOP = intraocular pressure.

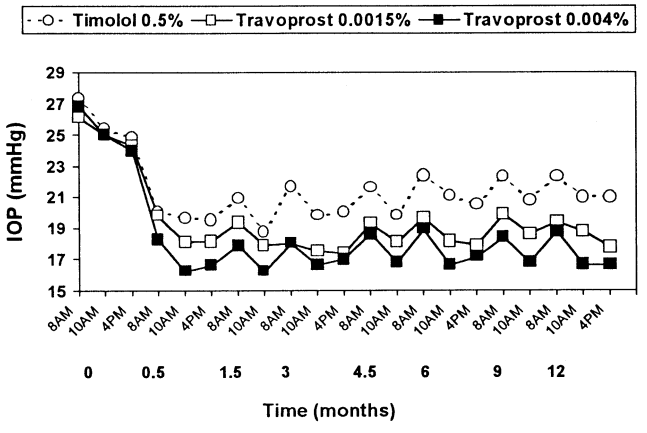

FIGURE 4. Mean intraocular pressure after travoprost 0.0015% and travoprost 0.004% compared with timolol 0.5% in black patients. The intraocular pressure was significantly lower after travoprost 0.0015% and 0.004% compared with timolol 0.5% in black patients (P = .0019 and P = .0001, respectively;, data pooled for all visits at 10:00 AM). IOP = intraocular pressure.

200) for timolol. However, the mean hyperemia score in all treatment groups was less than 1 on a scale of 0 to 3, indicating that on average the majority experienced between none/trace and mild hyperemia (Figure 6). Hyperemia assessment was performed at all time points (8 AM, 10 AM, and 4 PM), before intraocular pressure measurements and instillation of fluorescein. Hyperemia was subjectively graded in 0.5-U increments using a standard set of photographs depicting hyperemia, with 0 = none/trace, 1 = mild, 2 = moderate, and 3 = severe hyperemia.

In this study, the percentages of patients who experienced iris pigmentation changes were 5.0% (10 of 201) for travoprost 0.0015%, 3.1% (6 of 106) for travoprost 0.004%, and 5.2% (10 of 194) for latanoprost with none in the timolol group (Table 6). The majority of these changes occurred in individuals who had green-brown or blue/gray-brown irides at baseline. Changes in eyelash characteristics including length, thickness, density, and color were reported for 44.3% (89 of 201) and 57.1% (112 of 196) of patients in the travoprost 0.0015% and travoprost 0.004% groups, respectively. Eyelash changes were also reported in 25.8% (50 of 194) of patients in the latanoprost group and 3.1% (six of 196) of patients in the timolol group. Complaints related to eyelash changes were minimal (one patient in the 0.0015% group and one in the 0.004% group).

There were no clinically significant treatment differences in change from baseline for visual acuity, inflammatory cells and aqueous flare, ocular signs, fundus parameters, cup-to-disk ratio, or visual field parameters. In addition, there were no clinically significant differences in change from baseline for corneal thickness or endothelial cell count, and no cystoid macular edema was reported for any of the groups.

Although the mean change from baseline in pulse rate for timolol was significantly ($P \leq .0393$) greater than for travoprost and latanoprost, the difference (1.3 beats per minute) was not clinically significant, and there were no significant differences in systolic or diastolic blood pressure changes from baseline among groups. There were no clinically significant, treatment-related changes from baseline for laboratory values (hematology, blood chemistry, and urinalysis) among the treatment groups.

DISCUSSION

WHEN USED AS PRIMARY THERAPY, THE RESULTS OF THIS study show that both concentrations of travoprost

TABLE 4. Mean Intraocular Pressure Comparison of Travoprost (0.004% and 0.0015%) and Timolol 0.5%, by Race

	Baseline			Pooled			Week 2			Month 1.5		Month 3			Month 4.5		Month 6			Month 9		Month 12		
Treatment	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM
Black patients																								
Travoprost	26.8	25.0	24.0	18.4	16.5	16.7	18.3	16.2	16.6	17.9	16.2	18.0	16.6	17.0	18.7	16.8	18.9	16.6	17.1	18.4	16.8	18.8	16.7	16.6
0.004%																								
Timolol 0.5%	27.2	25.4	24.8	21.6	20.1	20.1	20.1	19.7	19.5	20.9	18.8	21.6	19.8	20.0	21.6	19.8	22.4	21.1	20.5	22.2	20.8	22.3	21.0	20.9
Difference	−0.5	−0.4	−0.8	−3.2	−3.6	−3.4	−1.8	−3.5	−2.9	−3.0	−2.7	−3.7	−3.2	−3.0	−2.9	−3.0	−3.5	−4.6	−3.4	−3.9	−4.0	−3.5	−4.3	−4.4
P value	0.4522	0.5018	0.2083	0.0001	0.0001	0.0001	0.0187	0.0001	0.0002	0.0001	0.0007	0.0001	0.0001	0.0001	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Travoprost	26.1	25.0	24.3	19.4	18.2	17.5	19.8	18.1	18.2	19.4	17.9	18.0	17.5	17.4	19.3	18.1	19.7	18.2	17.9	19.9	18.6	19.4	18.8	17.8
0.0015%																								
Timolol 0.5%	27.2	25.4	24.8	21.6	20.1	20.1	20.1	19.7	19.5	20.9	18.8	21.6	19.8	20.0	21.6	19.8	22.4	21.1	20.5	22.2	20.8	22.3	21.0	20.9
Difference	−1.2	−0.4	−0.4	−2.2	−2.0	−2.5	−0.3	−1.6	−1.4	−1.4	−1.0	−3.6	−2.3	−2.6	−2.2	−1.6	−2.7	−2.9	−2.6	−2.4	−2.2	−2.9	−2.1	−3.1
P value	0.0628	0.5340	0.4818	0.0004	0.0019	0.0006	0.6632	0.0405	0.0853	0.0728	0.2294	0.0001	0.0045	0.0011	0.0049	0.0395	0.0007	0.0003	0.0009	0.0028	0.0053	0.0003	0.0075	0.0001
Nonblack patients																								
Travoprost	26.8	25.2	24.7	19.3	18.3	18.1	19.1	18.0	17.8	19.2	17.9	19.0	18.2	18.0	19.1	18.3	19.3	18.2	18.3	19.6	18.7	20.0	18.6	18.4
0.004%																								
Timolol 0.5%	26.9	25.4	24.6	19.9	19.2	19.2	20.0	19.2	19.1	19.7	19.1	19.7	19.1	19.1	19.7	19.0	19.8	19.2	19.2	20.2	19.5	20.3	19.6	19.6
Difference	−0.1	−0.3	0.2	−0.6	−1.0	−1.1	−0.8	−1.2	−1.3	−0.5	−1.2	−0.7	−0.9	−1.1	−0.7	−0.7	−0.5	−1.1	−0.9	−0.7	−0.8	−0.3	−0.9	−1.2
P value	0.7687	0.4233	0.6346	0.0800	0.0037	0.0030	0.0465	0.0049	0.0025	0.2290	0.0052	0.0989	0.0318	0.0122	0.1205	0.0782	0.2407	0.0127	0.0253	0.1222	0.0534	0.5406	0.0281	0.0044
Travoprost	26.4	24.7	24.1	19.1	18.0	18.0	19.1	18.0	17.9	18.8	17.8	18.8	17.9	17.7	18.9	18.1	19.0	17.7	17.9	19.4	18.3	19.4	18.2	18.2
0.0015%																								
Timolol 0.5%	26.9	25.4	24.6	19.9	19.2	19.2	20.0	19.2	19.1	19.7	19.1	19.7	19.1	19.1	19.7	19.0	19.8	19.2	19.2	20.2	19.5	20.3	19.6	19.6
Difference	−0.5	−0.7	−0.5	−0.9	−1.2	−1.3	−0.9	−1.2	−1.2	−0.9	−1.3	−0.9	−1.2	−1.3	−0.8	−0.9	−0.8	−1.5	−1.3	−0.8	−1.2	−0.8	−1.4	−1.4
P value	0.1437	0.0373	0.1224	0.0096	0.0002	0.0009	0.0307	0.0043	0.0043	0.0268	0.0017	0.0338	0.0041	0.0012	0.0564	0.0295	0.0486	0.0003	0.0025	0.0408	0.0029	0.0488	0.0009	0.0006

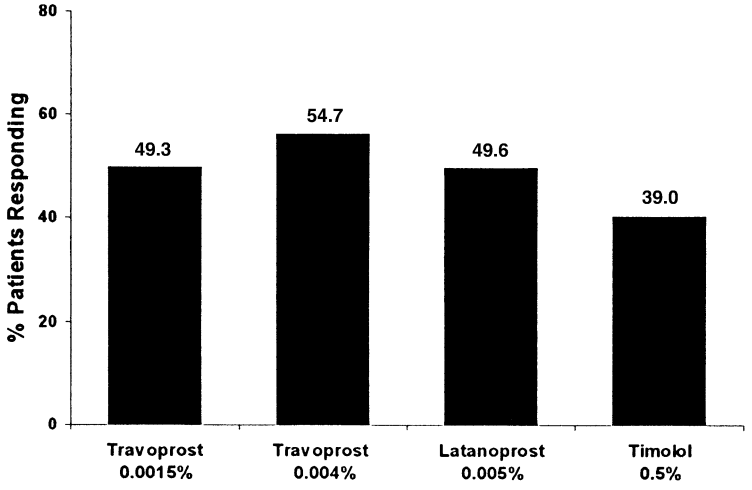

FIGURE 5. Responder analyses for travoprost, latanoprost, and timolol. The responder analyses were based on percent intraocular pressure reduction (30% or greater) or mean intraocular pressure (17 mm Hg or less). The differences between travoprost 0.004% compared with latanoprost 0.005% and timolol 0.5% were statistically significant ($P = 0.0430$ and 0.0001 or less, respectively).

TABLE 5. Frequency and Incidence of Adverse Events*

	Travoprost 0.0015% (n = 205)		Travoprost 0.004% (n = 200)		Timolol 0.5% (n = 200)		Latanoprost 0.005% (n = 196)	
	n	%	n	%	n	%	n	%
Ocular								
Hyperemia	78	38.0	99	49.5	28	14.0	54	27.6
Visual acuity decrease	12	5.9	17	8.5	19	9.5	9	4.6
Pain	6	2.9	16	8.0	3	1.5	7	3.6
Discomfort	11	5.4	15	7.5	15	7.5	5	2.6
Pruritis	8	3.9	15	7.5	4	2.0	12	6.1
Foreign body sensation	5	2.4	14	7.0	2	1.0	6	3.1
Cataract	10	4.9	14	7.0	7	3.5	6	3.1
Dry eye	5	2.4	9	4.5	3	1.5	2	1.0
Keratitis	5	2.4	7	3.5	5	2.5	4	2.0
Blepharitis	2	1.0	7	3.5	1	0.5	7	3.6
Blurred vision	1	0.5	6	3.0	6	3.0	9	4.6
Iris discoloration	10	4.9	6	3.0	0	0	10	5.1
Nonocular								
Surgical/medical procedure	22	10.7	19	9.5	24	12.0	26	13.3
Hypertension	12	5.9	13	6.5	9	4.5	7	3.6
Infection	9	4.4	11	5.5	14	7.0	10	5.1
Sinusitus	4	2.0	10	5.0	5	2.5	5	2.6
Accidental injury	6	2.9	8	4.0	5	2.5	4	2.0
Pain	5	2.4	8	4.0	6	3.0	3	1.5
Headache	4	2.0	8	4.0	5	2.5	5	2.6
Cold syndrome	9	4.4	6	3.0	7	3.5	2	1.0

*Includes all adverse events (related and nonrelated to treatment combined) reported at an incidence of at least 3.0%. All n values represent numbers of patients.

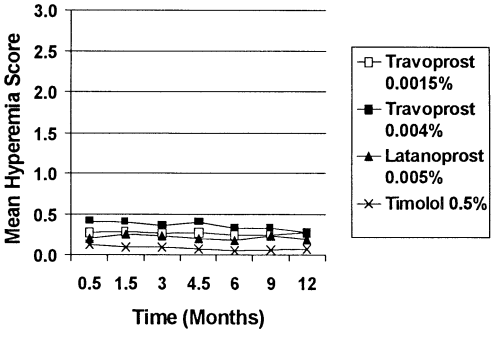

FIGURE 6. Average hyperemia scores for travoprost, latanoprost, and timolol. Hyperemia was graded at the 8:00 AM visit, with hyperemia scored as 0 = none to trace, 1 = mild, 2 = moderate, and 3 = severe. The mean hyperemia score was less than 1 in all treatment groups, indicating that the majority of patients experienced between none/trace to mild hyperemia.

(0.0015% and 0.004%) were equal or superior to latanoprost and superior to timolol in lowering intraocular pressure at all treatment visits in patients with open-angle glaucoma and ocular hypertension.

In studies carried out in the laser monkey model, reductions in intraocular pressure were observed beginning 2 hours after administration of travoprost and peaked by 12 to 20 hours after dose.[5] Although intraocular pressure measurements were not done 2 hours after the initial dose with travoprost, a significant reduction in intraocular pressure was evident early in the study, that is, within the first 2 weeks of treatment with travoprost. In addition, pooled results indicate that the intraocular pressure–low-

TABLE 6. Frequency and Incidence of Iris Pigmentation and Eyelash Changes*

	Travoprost 0.0015% (n = 201)	Travoprost 0.004% (n = 196)	Timolol 0.5% (n = 196)	Latanoprost 0.005% (n = 194)
Iris pigmentation change†				
n	10	6	0	10
%	5.0	3.1	0.0	5.2
Eyelash change‡				
n	89	112	6	50
%	44.3	57.1	3.1	25.8

*All patients randomized to treatment were included in the analysis of safety. Follow-up photographs to evaluate for iris pigmentation and eyelash changes were not available for four patients on travoprost 0.0015%, four patients on travoprost 0.004%, four patients on timolol 0.5%, and two patients on latanoprost 0.005%.

†$P = .014$ from chi-square test comparing treatment groups.

‡$P = .001$ from chi-square comparing treatment groups.

ering efficacy of travoprost was enhanced over the day from 8 AM to 4 PM and was significantly greater than latanoprost at 4 PM.

A conservative approach was taken in the analysis of intraocular pressure response to treatment using criteria of 30% or greater intraocular pressure reduction from diurnal baseline or a final intraocular pressure of 17 mm Hg or less. Whereas there was no difference in response rates between the travoprost 0.0015% and latanoprost groups, there was a 6.7% and 15.9% greater response rate in the travoprost 0.004% group than in the latanoprost and timolol groups, respectively, and this difference was statistically significant.

Although the most frequent adverse event reported in this study was ocular hyperemia, the majority of patients experienced between none/trace to mild hyperemia. Iris pigmentation change was observed at approximately the same rate in the travoprost and latanoprost groups. In addition, eyelash changes were also seen in the travoprost and latanoprost groups. These are cosmetic effects described previously for ocular prostaglandins[10] and did not appear to pose any safety issues to the patient or interfere with daily activities.

An interesting and unexpected finding of this study was the difference between black and nonblack patients in their response to medical therapy. Travoprost 0.004% reduced intraocular pressure in black patients by up to 2.4 mm Hg more than latanoprost. However, there was no difference in the intraocular pressure–lowering efficacy in the nonblack patients between travoprost 0.0015% and 0.004% and no significant difference between travoprost 0.0015% and latanoprost in lowering intraocular pressure for either black or nonblack patients. Only travoprost 0.004% produced lower mean intraocular pressure in the black population compared with travoprost 0.0015%, latanoprost and timolol. Reduction in mean intraocular pressure for black patients was even greater in the travoprost 0.004% group compared with the timolol group by up to 4.6 mm Hg in favor of travoprost 0.004%.

Studies have found that glaucoma and blindness from glaucoma are more prevalent in blacks than in whites[11,12] and is frequently more advanced at the time of diagnosis.[13,14] In the Baltimore Eye Survey, blacks were three to four times more likely than whites to have open-angle glaucoma[15] and the prevalence of blindness from glaucoma was six times as great in blacks.[11] In the Advanced Glaucoma Intervention Study black and white patients responded differently to surgical intervention.[16] Given the reported evidence that glaucoma has a different course in blacks than in whites and their different response to surgical therapy, it may not be surprising that these groups also react differently to medical therapy. Glaucoma is a common problem in the African American community and is the leading cause of blindness in this group in the United States.[11] Understanding the differences in the response to different antiglaucoma medications may enable clinicians to more effectively individualize optimal medical therapy for their patients.

The results from this study indicate that, when used as primary therapy, the intraocular pressure–lowering efficacy of travoprost (0.0015% and 0.004%) was equal or superior to that of latanoprost and superior to that of timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. In addition, travoprost 0.004% was significantly better than either latanoprost 0.005% or timolol 0.5% in lowering intraocular pressure in black patients.

TRAVOPROST STUDY GROUP

Cecil Beehler, MD, Eye Associates of Ft. Meyers, Ft. Meyers, FL 33901; John E. Bokosky, MD, San Diego, CA 92103; Robert Caine, MD, Eye Associates of Virginia, Fredericksburg, VA 22405; Delmar R. Caldwell, MD, Tulane University Medical Center, New Orleans, LA 70112; Carl Camras, MD, Univ of Nebraska Medical Center, Omaha, NE 68198; Louis B. Cantor, MD, Indiana University School of Medicine, Indianapolis, IN 46202-5175; Rudolf Churner, MD, Heritage Eye Center, McKinney, TX 75069; Douglas G. Day, MD, Omni Eye Services, Atlanta, GA 30342; Doug O. Dehning, MD, Eye Care, Inc., Blue Springs, MO 64014; Harvey B. DuBiner, MD, Clayton Eye Center, Morrow, GA 30260; Richard M. Evans, MD, Medical Center of Ophthalmology Associates, San Antonio, TX 78240; Robert M. Feldman, MD, Hermann Eye Center, Houston, TX 77030; Miles A. Galin, MD, East Side Ophthalmology, P.C., New York, NY 10016; Charles J. Henry, MD, Little Rock Eye Clinic, Little Rock, AR 72205; Michael S. Kottler, MD, Rocky Mountain Eye Center, Salt Lake City, UT 84107; Richard

A. Lewis, MD, Sacramento, CA 95819; Alan I. Mandell, MD, Eye Center of the Mid-South, Memphis, TN 38119; Wayne F. March, MD, University of Texas Galveston Medical Branch, Galveston, TX 77550; Frank J. Mares, MD, Eye Associates of New Mexico, Albuquerque, NM 87109; Thomas K. Mundorf, MD, Presbyterian Medical Center, Charlotte, NC 28204; Peter A. Netland, MD, PhD, University of Tennessee, Memphis, TN 38163; Kenneth W. Olander, MD, Maryville Eye Center, Maryville, TN 37803; Silvia Orengo-Nania, MD, Baylor College of Medicine, Houston, TX 77030; Douglas Ripkin, MD, Northeast Ohio Eye Surgeons, Kent, OH 44240; Michael H. Rotberg, MD, Charlotte Eye, Ear, Nose and Throat Associates, Charlotte, NC 28204; Kenneth N. Sall, MD, Sall Eye Surgery Center, Bellflower, CA 90706; Howard I. Schenker, MD, Rochester Ophthalmologic Group, P.C., Rochester, NY 14618; Todd D. Severin, MD, Optima Ophthalmic Medical Associates, Albany, CA 94706; Elizabeth D. Sharpe, MD, Ophthalmology Consultants, P.A., Mt. Pleasant, SC 29464; Dong H. Shin, MD, Kresge Eye Institute, Detroit, MI 48201; Paul A. Sidoti, MD, New York Eye and Ear Infirmary, New York, NY 10003; David E. Silverstone, MD, Temple Eye Physicians, New Haven, CT 06510; Shannon L. Smith, MD, Lehman Eye Center, Nacogdoches, TX 75961; Joseph W. Spadafora, OD, Community Eye Center, Port Charlotte, FL 33952; Robert L. Stamper, MD, Pacific Eye Associates, San Francisco, CA 94115; Onex D. Stevenson, MD, Stevenson Medical/Surgical Eye Center, New Orleans, LA 70119; Robert H. Stewart, MD, Houston Eye Associates, Houston, TX 77025; William C. Stewart, MD, Pharmaceutical Research Corp., Charleston, SC 29412; Michael C. Stiles, MD, Hunkler Eye Institute, Kansas City, MO 64111; Richard Sturm, MD, Long Island Ophthalmic Surgery Consultants, P.C., Lynbrook, NY 11563; George C. Thorne, MD, The Eye Institute of Austin, Austin, TX 78756; Jeffrey P. Wasserstrom, MD, Eye Associates of San Diego, La Mesa, CA 91942; Mark J. Weiss, MD, The Eye Institute, Tulsa, OK 74101; Robert D. Williams, MD, Taustine Eye Center, Louisville, KY 40217

REFERENCES

1. Bito LZ, Baroody RA. The ocular pharmacokinetics of eicosanoids and their derivatives. 1. Comparison of ocular eiconoid penetration and distribution following the topical application of PGF2 alpha, PGF2 alpha-1-methyl ester, and PGF2 alpha-1-isopropyl ester. Exp Eye Res 1987;44:217–226.
2. Hejkal TW, Toris CB, Camras CB. Prostaglandin analogs. In: Netland PA, Allen RC (editors). Glaucoma Medical Therapy: Principles and Management. San Francisco: The American Academy of Ophthalmology, 1999, pp. 113–131.
3. Sharif NA, Davis TL, Williams GW. [3H]AL-5848 ([3H]9beta-(+)-Fluprostenol). Carboxylic acid of travoprost (AL-6221), a novel FP prostaglandin to study the pharmacology and autoradiographic localization of the FP receptor. J Pharm Pharmacol 1999;51:685–694.
4. Davis TL, Sharif NA. Quantitative autoradiographic visualization and pharmacology of FP-prostaglandin receptors in human eyes using the novel phosphor-imaging technology. J Ocul Pharmacol Ther 1999;15:323–336.
5. Hellberg MR, Sallee V, McLaughlin MA, et al. Preclinical efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist. J Ocular Pharm Ther. Forthcoming.
6. Garadi R, Silver L, Landry T, Turner FD. Travoprost: a new once-daily dosed prostaglandin for the reduction of elevated intraocular pressure. Invest Ophthalmol Vis Sci 1999;40: S831.
7. The European Agency for the Evaluation of Medicinal Products. ICH Topic E9, statistical principles for clinical trials. Document CPMP/ICH/363/96. September 1998.
8. The European Agency for the Evaluation of Medicinal Products. Points to consider on switching between superiority and non-inferiority. Document CPMP/EWP/482/99. July 2000.
9. Westfall P, Tobias R, Rom D, Wolfinger R, Hochberg Y. Multiple comparisons and multiple tests using the SAS System. Cary, NC: SAS Institute, 1999:35–37.
10. Patel SS, Spencer CM. Latanoprost. A review of its pharmacological properties, clinical efficacy and tolerability in the management of primary open-angle glaucoma and ocular hypertension. Drugs Aging 1996;9:363–378.
11. Sommer A, Tielsch JM, Katz J, et al. Racial differences in the cause-specific prevalence of blindness in East Baltimore. N Engl J Med 1991;325:1412–1417.
12. Hiller R, Kahn HA. Blindness from glaucoma. Am J Ophthalmol 1975;80:62–69.
13. Wilson R, Richardson TM, Hertzmark, E, Grant WM. Race as a risk factor for progressive glaucomatous damage. Ann Ophthalmol 1985;17:653–659.
14. Martin MJ, Sommer A, Gold EB, Diamond EL. Race and primary open-angle glaucoma. Am J Ophthalmol 1985;99: 383–387.
15. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of open-angle glaucoma. The Baltimore Eye Study. JAMA 1991;266:369–374.
16. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within race. Seven-year results. Ophthalmology 1998;105:1146–1164.