A Comparison of Latanoprost, Bimatoprost, and Travoprost in Patients With Elevated Intraocular Pressure: A 12-week, Randomized, Masked-evaluator Multicenter Study

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• PURPOSE: To compare the intraocular pressure (IOP)-lowering effect and safety of latanoprost, bimatoprost, and travoprost in patients with open-angle glaucoma (OAG) or ocular hypertension (OH).

• DESIGN: Interventional study.

• METHODS: This 12-week, randomized, parallel-group study was conducted at 45 US sites. Previously treated patients with OAG or OH and an IOP ≥23 mm Hg in one or both eyes after washout received either latanoprost 0.005%, bimatoprost 0.03%, or travoprost 0.004% once daily in the evening. At baseline and after 6 and 12 weeks of therapy, masked evaluators measured IOP in triplicate at 8:00 AM, 12 noon, 4:00 PM, and 8:00 PM, and masked investigators graded conjunctival hyperemia before the 8:00 AM IOP measurement. The primary efficacy outcome measure was change between baseline and Week 12 in the 8:00 AM IOP (time of peak drug effect).

• RESULTS: In all, 410 of 411 randomized patients were included in intent-to-treat analyses (latanoprost, 136; bimatoprost, 136; travoprost, 138). Baseline mean 8:00 AM IOP levels were similar ($P = .772$); by week 12, reductions were observed in all 3 groups ($P < .001$ for each). Adjusted (ANCOVA) reductions in mean IOP at 8:00 AM were similar ($P = .128$) as were those at 12 noon, 4:00 PM, and 8:00 PM. Fewer latanoprost-treated patients reported ocular adverse events ($P < .001$, latanoprost vs bimatoprost), fewer reported hyperemia ($P = .001$, latanoprost vs bimatoprost), and average hyperemia scores were lower at week 12 ($P = .001$, latanoprost vs bimatoprost).

• CONCLUSIONS: Latanoprost, bimatoprost, and travoprost were comparable in their ability to reduce IOP in OAG and OH patients. Latanoprost exhibited greater ocular tolerability. (Am J Ophthalmol 2003;135: 688–703. © 2003 by Elsevier Inc. All rights reserved.)

AMONG THE CURRENT OCULAR HYPOTENSIVE MEDIcations employed in the treatment of open-angle glaucoma and ocular hypertension, prostaglandin analogues are the most potent.[1] These include the prostaglandin analogues latanoprost, bimatoprost, travoprost, and unoprostone. In the United States, latanoprost has been commercially available since 1996, with bimatoprost, travoprost, and unoprostone receiving Food and Drug Administration (FDA) approval between August 2000 and March 2001.[2] Although the precise mechanism used by these agents to lower intraocular pressure (IOP) is unclear, they are believed to act by increasing aqueous humor outflow through both the trabecular route (via Schlemm's canal and the episcleral veins) and the uveoscleral (ciliary muscle) pathway.[3–9]

Latanoprost (0.005%), bimatoprost (0.03%), and travoprost (0.004%) have been shown to be as or more effective in lowering IOP than the traditional first-line agent and standard of reference, timolol 0.5%.[10–14] Unoprostone, however, has been shown to be less effective in lowering IOP than latanoprost[15,16] and not to be more effective than timolol.[17–19] Although there is extensive documentation concerning the efficacy of the three prostaglandin analogues, especially latanoprost,[20] data determining the comparative efficacy of the three drugs in a single trial have not been reported.

The majority of the studies that compared the efficacy and safety of latanoprost and travoprost[14] or of latanoprost and bimatoprost[21,22] have shown no clinically significant

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differences in the IOP-lowering ability of these medications at 8 AM, the time of peak effect, and differences at other time points may have been confounded by baseline differences. The exception was a recent investigation[23] suggesting that bimatoprost may be more effective than latanoprost in reducing IOP levels. Less open to debate has been the relative frequency of several ocular adverse events, most notably ocular hyperemia, which may affect patient compliance and thus the overall effectiveness of the topical prostaglandin analogues. Compared to latanoprost, both bimatoprost and travoprost have been shown to have substantially higher rates of ocular side effects.[14,22] The present trial is the first to compare simultaneously the clinical outcomes associated with the use of latanoprost, bimatoprost, and travoprost.

METHODS

• **SETTING:** This 12-week, randomized, parallel-group, masked-evaluator study conducted at 45 sites in the United States compared the efficacy and safety of once daily administration of three commercially available prostaglandin analogues: latanoprost 0.005%, bimatoprost 0.03%, and travoprost 0.004% ophthalmic solutions. Regulatory authorities at each study site reviewed and approved the protocol in accordance with guidelines for the conduct of clinical research contained in the 1964 Declaration of Helsinki.

• **PATIENTS:** Patients were eligible for participation if they met the following inclusion criteria: age ≥ 18 years; bilateral or unilateral primary open-angle glaucoma, exfoliative glaucoma, pigmentary glaucoma, or ocular hypertension (IOP ≥ 21 mm Hg at diagnosis); current or previous (within the past 6 months) monotherapy or dual therapy with a topical ocular hypotensive agent(s); best-corrected visual acuity equal to or better than 20/200; and ability to comply with the requirements of the study protocol. All patients provided signed informed consent prior to study enrollment.

Exclusion criteria were known hypersensitivity to any component in the study medications; use of any medication known to affect IOP unless both patient and dosage were stable within the previous 3 months and no change in dosage was expected during the study; use of any investigational medications within 30 days of the screening visit; history of acute angle-closure or closed or slit open anterior chamber angle; argon laser trabeculoplasty or other ocular (globe) surgery within the previous 3 months or any previous filtering surgery (an unlasered or unfiltered eye could be enrolled as the study eye); ocular infection or inflammation within the previous 3 months; and pregnancy, lactation, or inadequate contraception.

• **TREATMENT PROTOCOL:** A screening visit examination for all patients (up to 1 month prior to the baseline visit) included a review of ocular and medical history, IOP measurement with a calibrated Goldmann applanation tonometer, Snellen visual acuity measurement, slit-lamp biomicroscopy, ophthalmoscopy, and visual field testing (automated perimetry) if not done within the past 12 months. Patients deemed eligible for the study were removed from all ocular hypotensive therapy at this time. Required washout periods prior to the baseline visit were 5 days for cholinergic agonists and carbonic anhydrase inhibitors; 2 weeks for adrenergic agonists; and 4 weeks for β-adrenergic receptor antagonists and prostaglandin analogues. For all patients previously using β-adrenergic receptor antagonists and prostaglandin analogues, IOP measurement was required as a safety check after 2 weeks of washout; observed IOP levels considered potentially hazardous resulted in patients being excluded from the study.

Study visits occurred at baseline and after 2, 6, and 12 weeks of therapy. At the baseline visit, which followed the washout period, masked evaluators performed three IOP measurements in each eye, alternating between eyes, and starting with the right eye at 8:00 AM, 12 noon, 4:00 PM, and 8:00 PM. The mean of these IOP measurements at each time point was used in statistical analyses. Either one or both eyes of a patient could be enrolled as study eyes. An eye was eligible if the mean IOP was ≥23 mm Hg at the 8:00 AM baseline measurement. For patients having both eyes enrolled, the mean of the IOP readings in both eyes was used as the patient's IOP in the analyses. In patients with bilateral disease with only one eye that met all eligibility criteria (study eye), the other eye also could be treated with study drug provided that no exclusion criteria existed for that eye. If both eyes met all eligibility criteria, both were enrolled as study eyes.

Study medications were packaged in commercially available labeled containers manufactured by Pharmacia Corporation (latanoprost), Allergan (bimatoprost), and Alcon Laboratories (travoprost). To preserve masking, each container was overpackaged in an opaque black vial and then sealed in a patient kit with tamper-evident strips; the name of the drug was not included on kit labels. A designated, unmasked coordinator (who did not perform any study evaluations or assessments) at each study center received randomization codes and prepackaged clinical supplies from Pharmacia Clinical Supply Logistics (Kalamazoo, Michigan, USA), and dispensed the medication kits. The coordinator was responsible for storing each medication kit according to its respective product package insert.

Following the 8:00 PM baseline measurement, eligible patients were randomly assigned within each study center to one of three treatment groups in a 1:1:1 ratio: latanoprost 0.005%, bimatoprost 0.03%, or travoprost 0.004%. One patient medication kit was dispensed to each eligible patient at the baseline visit and another at the week 6

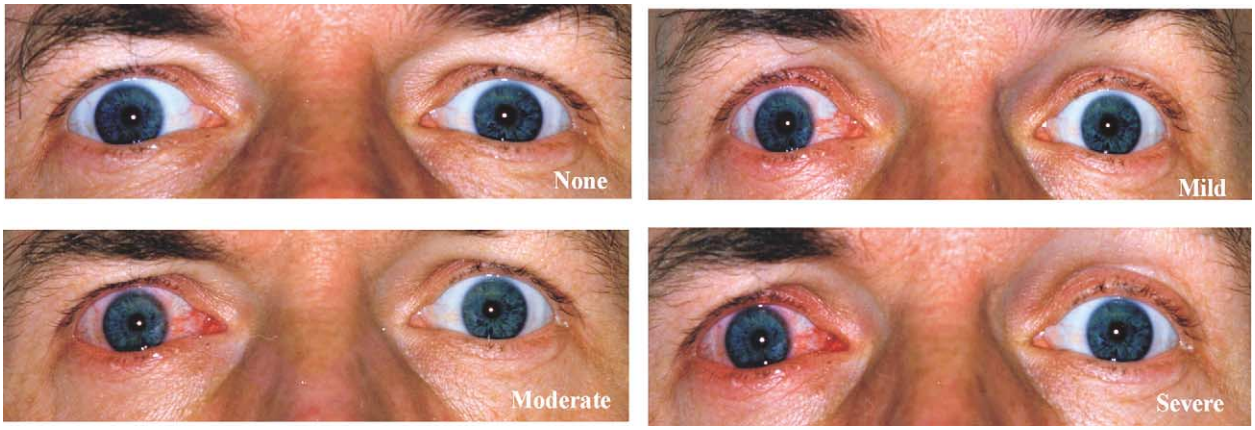

FIGURE 1. Standard photographs used to assess grades of conjunctival hyperemia.

visit; patients were instructed to return all study medications at week 12 or at the final visit for those discontinuing the study early. Patients were reminded to change study medication bottles every 4 weeks. Each medication was to be instilled daily at 8:00 PM, and no other IOP-reducing therapy was permitted. Instillation of study medication began on the evening of the baseline visit. Physician investigators (hereafter called investigators) and evaluators remained masked to treatment throughout the study; patients were the only ones aware of their treatment assignments and were cautioned not to reveal the treatment assignment to masked study-site personnel. At weeks 2, 6, and 12, investigators noted on the case report form whether or not masking had been maintained. The statistician also was masked until the database was closed.

Intraocular pressure was measured at any time during the day at week 2 and at 8:00 AM, 12 noon, 4:00 PM, and 8:00 PM at weeks 6 and 12 (or at time of earlier discontinuation). As at baseline, masked evaluators performed three IOP measurements in each eye, alternating between eyes, and starting with the right eye at each specified time point. At weeks 6 and 12, patients were questioned to ensure that the last eyedrop was administered the evening before the visit. The mean of the three IOP measures for each eye at each time point was used in statistical analyses.

At baseline and weeks 6 and 12, an investigator masked to treatment completed a conjunctival hyperemia grading scale before the 8:00 AM IOP measurement; at week 2, grading was performed prior to tonometry. The presence and severity of hyperemia were assessed by the method used in several phase 3 registration trials.[10–12] Each eye was compared with standard photographs showing conjunctival hyperemia of grades 0, 1, 2, and 3 (none, mild, moderate, and severe, respectively) (Figure 1); the scale included values of 0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0. In addition, at every visit, the same investigator asked patients whether they or anyone else had noticed any redness in his or her eye(s) since the last visit and, if so, to what extent they were bothered by such redness. Extent of symptom was graded with the following responses: not at all, a small amount, a moderate amount, or a great amount. Investigators recorded patients' responses.

Throughout the study, any undesired medical occurrence regardless of relationship to treatment was considered an adverse event and was monitored. Defined criteria were used to grade the intensity of each adverse event and to classify the event as serious or nonserious. Any adverse event considered serious, related to study medication and persistent, or any ocular adverse event present at the end of study treatment (week 12) resulted in patients being followed up for 2 weeks after the final visit. Follow-up of serious adverse events considered to be related to a study medication continued until events were resolved or deemed chronic or stable.

• **MAIN OUTCOME MEASURES AND ANALYSES:** The Fisher least significant difference procedure was used to compare treatment groups.[24] Continuous variables were tested for treatment group differences using one-way analysis of variance (ANOVA) with treatment (latanoprost, bimatoprost, or travoprost) as the independent variable. If the overall treatment effect was not significant ($P > .05$), it was concluded that no difference existed between treatment means. If the overall treatment effect was significant ($P \leq .05$), pairwise comparisons of treatment means were performed using t tests, with the significance of each set at the .05 level.

The primary efficacy outcome, mean change between baseline and week 12 in IOP measurements obtained at 8:00 AM (time of peak drug effect), was analyzed using the above procedure, but with the analysis of covariance model (ANCOVA), with baseline IOP as the covariate and treatment and center as factors. If the overall treatment effect was significant, pairwise comparisons of treatment means were performed using contrasts. The 95% confidence interval (CI) of the difference in the mean change was calculated based on the ANCOVA model. This procedure also was applied to the secondary outcomes,

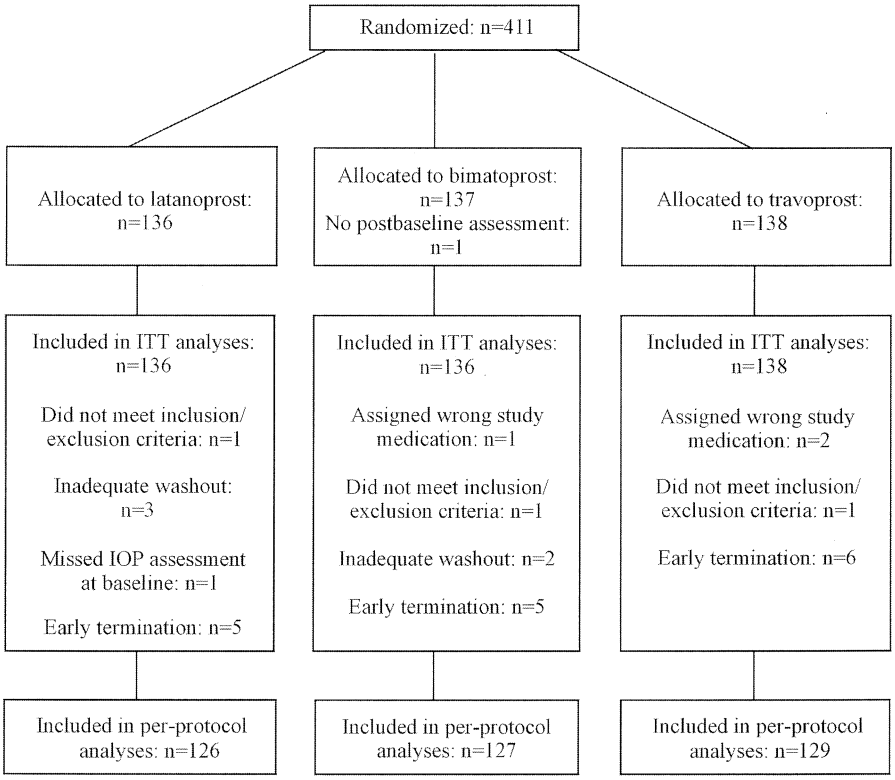

FIGURE 2. Flow diagram of patient disposition. IOP = intraocular pressure; ITT = intent-to-treat.

mean change between baseline and week 12 in IOP measurements obtained at 12 noon, 4:00 PM, and 8:00 PM (time of trough), and in diurnal IOP, which was defined as the mean of IOP measurements at 8:00 AM, 12 noon, 4:00 PM, and 8:00 PM. Within-treatment group IOP changes were tested with paired *t* tests. Categorical variables are presented in contingency tables with counts and percentages, and a Fisher exact test or chi-square test was used to test for treatment group differences. All statistical tests were two-tailed and were performed at the .05 significance level.

Racial differences in treatment response also were analyzed using the ANCOVA model, with change from baseline to week 12 in 8:00 AM IOP as the dependent (outcome) variable, baseline 8:00 AM IOP as the covariate, and treatment, center, race, and treatment-by-race interaction as other factors. Race was categorized as Caucasian, black, and other for this analysis. A similar analysis was conducted on IOP change between baseline and week 12 in 8:00 PM IOP.

Separate and parallel efficacy analyses of both intent-to-treat (ITT) and per-protocol populations were conducted. All efficacy analyses were based on study eye(s). The ITT analyses included all randomized patients who had at least one valid IOP evaluation after beginning treatment with study medication. For ITT analyses, missing IOP measurements at week 12 were obtained by carrying forward the corresponding week 6 measurements. Diurnal IOP then was calculated based on available measurements. If no measurement was available, the diurnal measurement at the previous visit was carried forward. Missing values at week 6 were imputed using week 2 data. Although 2.1% of the 5,330 expected IOP observations were missing, per-protocol analyses that excluded patients who did not complete the study or who had major protocol violations also were conducted to confirm ITT results. Those analyses included all patients who completed the full course of treatment without a major violation of protocol guidelines; no missing data were imputed for the per-protocol analyses.

Safety analyses included all randomized patients (safety population). The Medical Dictionary for Regulatory Activities (MedDRA) coding system was used to classify adverse events. Frequencies of ocular and systemic adverse events and numbers of patients affected were summarized by treatment group. Ocular adverse events and hyperemia events (MedDRA preferred terms: ocular hyperemia, red eye, conjunctival vascular disorder not otherwise specified, and conjunctivitis not elsewhere classified) also were summarized by maximum intensity. Masked investigators' and patients' assessments of hyperemia were summarized by treatment and visit and were tested for treatment differences. Each patient's hyperemia score was calculated by taking the mean of the hyperemia scores of the patient's treated eyes. Other safety variables, such as visual acuity,

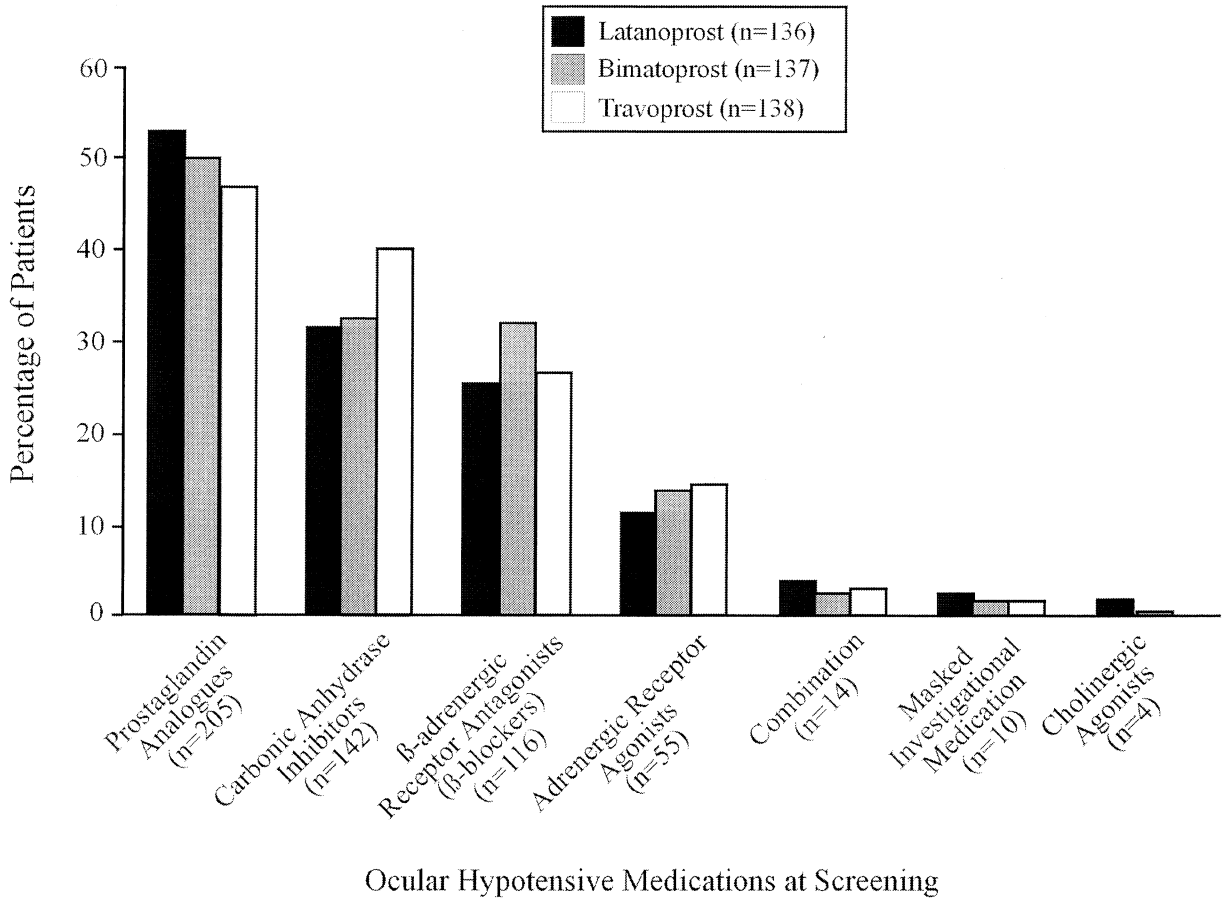

FIGURE 3. Frequencies of patients receiving intraocular pressure (IOP)-reducing medication at screening (intent-to-treat population). Some patients were taking dual therapy.

changes after treatment in the lid and slit-lamp examination, and ophthalmoscopy results, also were tabulated.

Before the study, it was determined that a sample of at least 113 patients capable of being evaluated per treatment group was required to detect a difference of 1.5 mm Hg in mean IOP reduction between the two treatment groups at a significance level of .05, with a power of .80 and assuming a standard deviation (SD) of 4.0 mm Hg. The plan was to include a minimum of 375 patients so as to allow for patient withdrawals.

RESULTS

• **PATIENT DISPOSITION AND DEMOGRAPHICS:** In all, 514 patients were screened; 1 patient was excluded at the week 2 safety check because of an elevated IOP. Following enrollment at baseline, 411 patients were randomized to three treatment groups: latanoprost (n = 136), bimatoprost (n = 137), and travoprost (n = 138) (Figure 2). One patient in the bimatoprost group received medication but had no postbaseline evaluation and was excluded from ITT analyses. The resulting ITT population comprised 410 patients of whom 172 (42.0%) were male, 229 (55.9%) were Caucasian, and 125 (30.5%) were African American. Diagnoses included primary open-angle glaucoma in 309/410 (75.4%) patients, ocular hypertension in 95/410 (23.2%) patients, and exfoliative or pigmentary glaucoma in 5/410 (1.2%) patients; 1 patient had none of the listed diagnoses. Study participants had a mean age of 65 years. At screening, the latanoprost, bimatoprost, and travoprost ITT groups had similar proportions of patients taking a prostaglandin analogue (52.9%, 49.6%, and 47.1%, respectively) (Figure 3), and those taking a prostaglandin had similar mean IOP levels (19.4 mm Hg, 19.6 mm Hg, and 19.9 mm Hg, respectively) (Figure 4). Demographic and baseline characteristics were generally similar across treatment groups with no statistically significant differences found (Table 1). Overall, 98/136 (72.1%) of latanoprost-treated patients, 96/136 (70.6%) patients receiving bimatoprost, and 79/138 (57.2%) of those treated with travoprost had both eyes as study eyes, and 400/410 (97.6%) patients received assigned study medication in both eyes (one eye of which may not have been a study

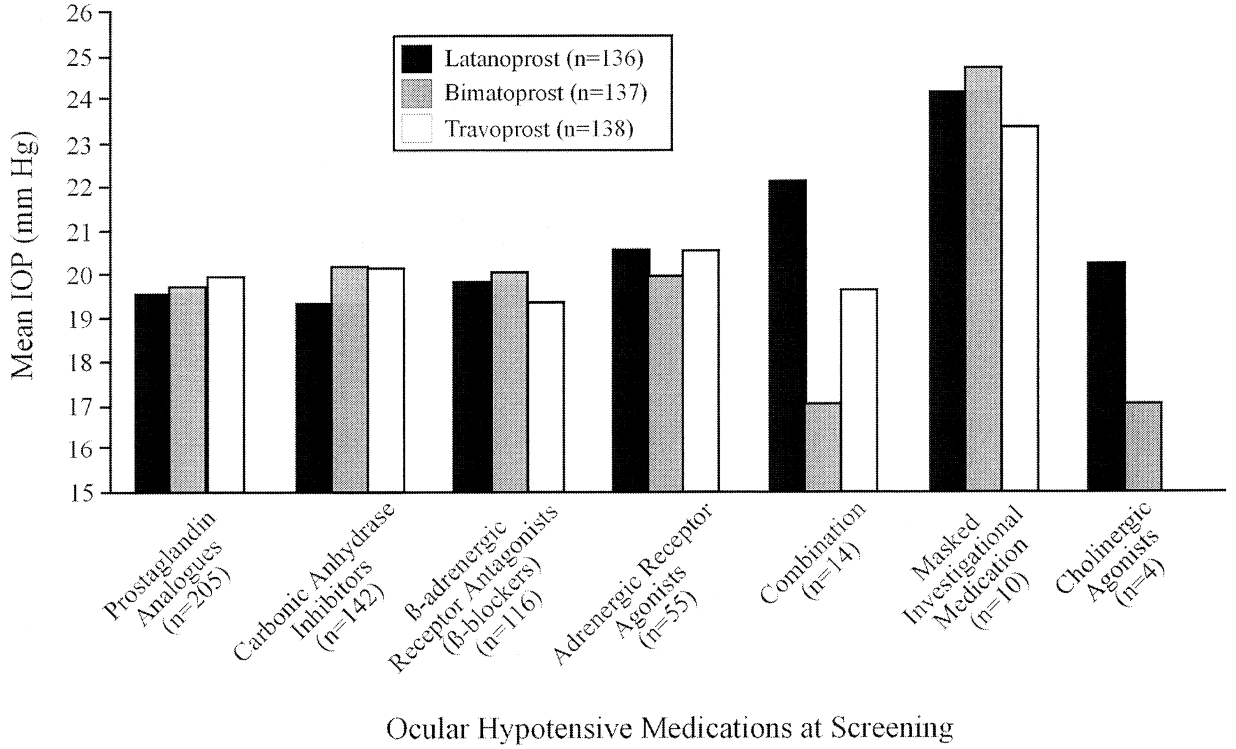

FIGURE 4. Mean intraocular pressure (IOP) at screening by IOP-reducing medication (intent-to-treat population). Some patients were taking dual therapy.

eye). Of the 393/411 patients (95.6%) who completed the study, the average exposure to study medication was 86 days, including the baseline day.

Unmasking occurred in 6 patients (latanoprost, n = 3; bimatoprost, n = 1; travoprost, n = 2); in 3 of these cases, the technician was unmasked but the investigator was not. In all, 28/410 (6.8%) patients (latanoprost, n = 10; bimatoprost, n = 9; travoprost, n = 9) included in ITT analyses were excluded from per-protocol evaluations owing to major protocol deviations, early termination from the study, or both (Figure 2). Demographic characteristics and efficacy results of primary and secondary endpoints were similar in ITT and per-protocol populations.

• **EFFICACY RESULTS:** At baseline, mean IOP levels were similar across groups at each time point and for the diurnal measurement (Table 2; Figures 5 and 6). With regard to the primary efficacy variable, mean 8:00 AM IOP levels at baseline were 25.7 mm Hg in the latanoprost group, 25.7 mm Hg in the bimatoprost group, and 25.5 mm Hg in the travoprost group ($P = .772$). By week 12, significant ($P < .001$) reductions were observed in all three treatment groups. The estimated mean ± SEM IOP reduction (ANCOVA) was 8.6 ± 0.3 mm Hg for those treated with latanoprost, 8.7 ± 0.3 mm Hg for bimatoprost-treated patients, and 8.0 ± 0.3 mm Hg for patients receiving travoprost ($P = .128$ for difference among groups). Adjusted differences (see Methods) in mean IOP reductions at 8:00 AM also showed equivalence among treatments when latanoprost was compared with either bimatoprost (latanoprost versus bimatoprost: −0.13 mm Hg; 95% CI −0.84, 0.58) or with travoprost (latanoprost vs travoprost: 0.56 mm Hg; 95% CI −0.15, 1.26) and when bimatoprost was compared with travoprost (bimatoprost vs travoprost: 0.69 mm Hg; 95% CI −0.02, 1.40).

The distributions of changes in IOP levels for the primary efficacy variable for each treatment group are given in Figure 7. Inspection of the distributions reveals quite similar box plots. Subgroup analyses for each treatment group, stratified by previous use or nonuse of a prostaglandin analogue (Figure 8A) or by the occurrence or nonoccurrence of investigator-noted hyperemia (Figure 8B), similarly do not reveal differences.

Results of per-protocol analyses of changes from baseline to week 12 in mean IOP levels at 8:00 AM generally were supportive of those of ITT evaluations, although the overall treatment difference was significant ($P = .029$, ANCOVA). Adjusted differences (see Methods) in mean IOP reductions at 8:00 AM showed comparability between latanoprost and either bimatoprost (−0.22 mm Hg; 95% CI −0.94, 0.50) or travoprost (0.71 mm Hg; 95% CI −0.01, 1.42), but IOP levels were reduced more in bimatoprost-treated than in travoprost-treated patients (0.93 mm Hg; 95% CI 0.22, 1.65).

Mean IOP levels at week 12 were similar across treatment groups at all time points (Figure 6). The ITT analyses

TABLE 1. Demographic Data (Intent-to-Treat Population)

	Latanoprost (n = 136)	Bimatoprost (n = 136)	Travoprost (n = 138)
	n (%)	n (%)	n (%)
Gender			
Male	60 (44.1)	52 (38.2)	60 (43.5)
Age (year)			
Mean (SD)	65.9 (11.27)	64.4 (12.35)	65.6 (10.81)
Range	28–90	29–85	26–82
Ethnic origin			
Caucasian	72 (52.9)	74 (54.4)	83 (60.1)
African American	40 (29.4)	45 (33.1)	40 (29.0)
Hispanic	20 (14.7)	12 (8.8)	13 (9.4)
Asian	4 (2.9)	3 (2.2)	2 (1.4)
Other	0	2 (1.5)	0
Eye color			
Homogeneously blue, gray, or green	33 (24.3)	35 (25.7)	40 (29.0)
Homogeneously brown	92 (67.6)	88 (64.7)	82 (59.4)
Blue-brown/gray-brown	5 (3.7)	3 (2.2)	4 (2.9)
Green-brown	6 (4.4)	7 (5.1)	9 (6.5)
Yellow-brown	0	3 (2.2)	3 (2.2)
Nevi or freckles (study eye[s])			
On iris	22 (16.2)	17 (12.5)	25 (18.1)
On conjunctiva bulbi	12 (8.8)	10 (7.4)	5 (3.6)
On both	2 (1.5)	2 (1.5)	0
Not present	100 (73.5)	107 (78.7)	108 (78.3)
Diagnosis (study eye[s])			
Primary open-angle glaucoma	105 (77.2)	103 (75.7)	101 (73.2)
Pigmentary glaucoma	1 (0.7)	1 (0.7)	1 (0.7)
Exfoliative glaucoma	1 (0.7)	1 (0.7)	0
Ocular hypertension	29 (21.3)	31 (22.8)	35 (25.4)
None of listed diagnoses	0	0	1 (0.7)
Duration of condition (study eye[s])			
≤6 months	12 (8.8)	6 (4.4)	10 (7.2)
>6 to 36 months	44 (32.4)	35 (25.7)	47 (34.1)
>36 to 120 months	55 (40.4)	72 (52.9)	55 (39.9)
>120 months	25 (18.4)	23 (16.9)	26 (18.8)
Family history of glaucoma/ocular hypertension	50 (36.8)	53 (39.0)	58 (42.0)
Visual field—any glaucomatous defect (study eye[s])	70 (51.5)	66 (48.5)	63 (45.7)
Baseline IOP-lowering medications*			
Prostaglandin analogues	72 (52.9)	68 (50.0)	65 (47.1)
Carbonic anhydrase inhibitors	43 (31.6)	44 (32.4)	55 (39.9)
β-Adrenergic receptor antagonists	35 (25.7)	44 (32.4)	37 (26.8)
Adrenergic receptor agonists	16 (11.8)	19 (14.0)	20 (14.5)
Combination therapies	5 (3.7)	4 (2.9)	5 (3.6)
Masked investigational drugs	4 (2.9)	3 (2.2)	3 (2.2)
Cholinergic agonists	3 (2.2)	1 (0.7)	0

IOP = intraocular pressure.
*Some patients were receiving dual therapy at baseline.

revealed no significant differences among treatment groups in adjusted mean IOP reductions from baseline to week 12 at 12 noon, 4:00 PM, or 8:00 PM ($P = .075$, $P = .057$, and $P = .100$, respectively). Also, no significant difference existed across treatments in changes in mean diurnal IOP levels measured at week 12 ($P = .125$); distributions of diurnal IOP reductions from baseline to week 12 are shown in Figure 7.

In an exploratory analysis, no racial differences in patients' responses to the treatments were observed; however, the study was not powered to detect subgroup differences based on race. The ANCOVA model, using

TABLE 2. Intraocular Pressure (IOP) and IOP Reduction From Baseline to Week 12: Unadjusted Mean ± SD (Intent-to-Treat Population)

	IOP (mm Hg)			IOP Reduction (mm Hg): Baseline to Week 12		
	Latanoprost (n = 136)	Bimatoprost (n = 136)	Travoprost (n = 138)	Latanoprost (n = 136)	Bimatoprost (n = 136)	Travoprost (n = 138)
Baseline						
8:00 AM	25.7 ± 2.8	25.7 ± 3.1	25.5 ± 2.8			
12 noon	23.7 ± 3.5	23.8 ± 3.4	23.8 ± 3.8			
4:00 PM	23.0 ± 3.6	22.8 ± 3.6	22.8 ± 3.3			
8:00 PM	22.3 ± 3.7	22.3 ± 3.3	22.0 ± 3.4			
Diurnal	23.7 ± 2.9	23.7 ± 2.7	23.5 ± 2.9			
Week 12						
8:00 AM	17.1 ± 3.1	17.0 ± 3.3	17.6 ± 3.7	8.6 ± 3.7	8.7 ± 3.8	7.9 ± 3.4
12 noon	16.5 ± 2.7	16.2 ± 3.0	16.8 ± 3.3	7.2 ± 3.9	7.6 ± 4.0	6.8 ± 3.6
4:00 PM	16.7 ± 2.5	16.0 ± 2.8	16.4 ± 3.4	6.2 ± 3.6	6.8 ± 4.0	6.3 ± 3.8
8:00 PM	16.3 ± 2.4	15.8 ± 3.0	16.1 ± 3.2	5.9 ± 3.8	6.5 ± 3.4	5.7 ± 3.9
Diurnal	16.7 ± 2.4	16.4 ± 2.8	16.8 ± 3.2	7.0 ± 3.1	7.3 ± 3.2	6.7 ± 3.2

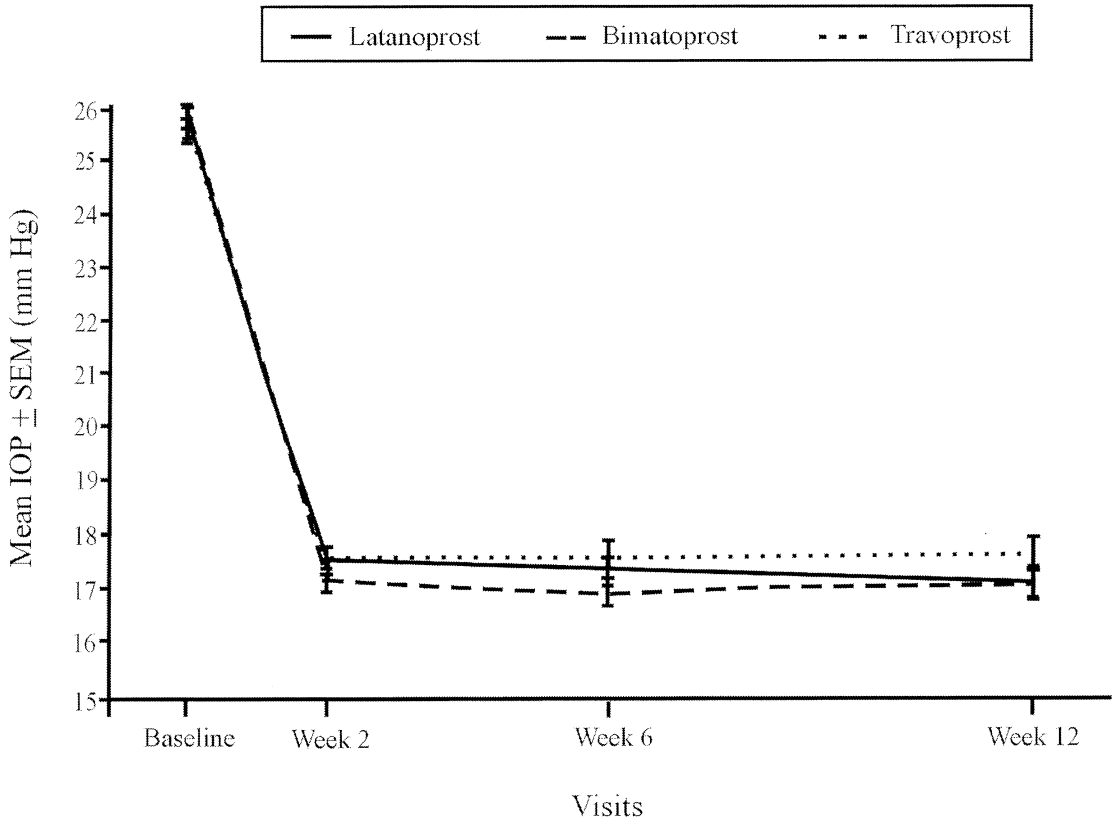

FIGURE 5. Unadjusted 8:00 AM mean intraocular pressure (IOP) levels by treatment and visit (intent-to-treat population).

change in IOP between baseline and week 12 as the dependent variable, yielded no evidence for race effect ($P = .439$, 8:00 AM; $P = .227$, 8:00 PM) or treatment by race effect ($P = .681$, 8:00 AM; $P = .543$, 8:00 PM).

• **SAFETY RESULTS:** At least one adverse event was reported by 87/136 (64.0%) patients receiving latanoprost, 104/137 (75.9%) of those in the bimatoprost group, and 95/138 (68.8%) of those treated with travoprost (Table 3). Fewer latanoprost-treated patients reported an ocular adverse event compared with those receiving bimatoprost or travoprost ($P = .003$ for difference among the three treatments; $P < .001$ for difference between latanoprost and bimatoprost). Compared with latanoprost-treated or

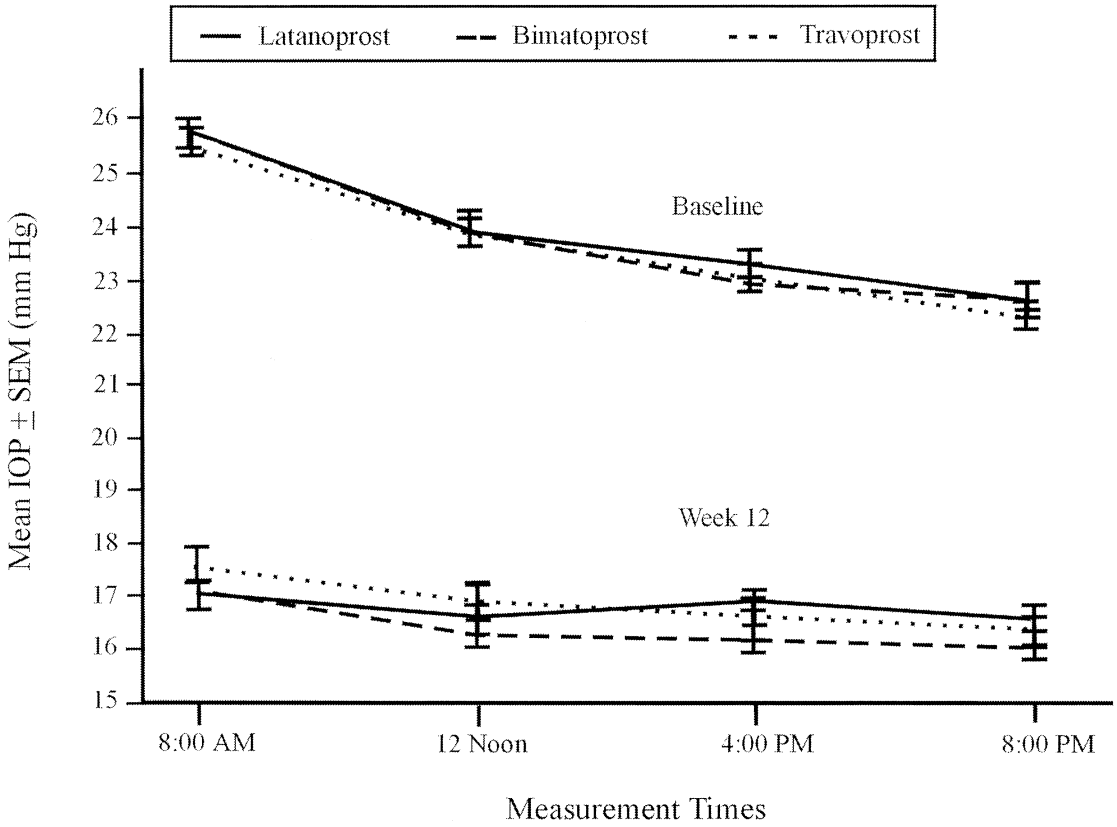

FIGURE 6. Unadjusted mean intraocular pressure (IOP) levels by treatment and measurement time at baseline and week 12 (intent-to-treat population).

travoprost-treated patients, a larger proportion of those treated with bimatoprost reported an adverse event related to a study medication ($P = .015$ for difference among the three treatments; $P < .001$ for difference between latanoprost and bimatoprost).

Table 4 summarizes ocular adverse events reported by more than 2% of patients in any treatment group. The most frequently reported events were hyperemia and eye irritation. In all, 94/137 (68.6%) bimatoprost patients, 80/138 (58.0%) travoprost patients, and 64/136 (47.1%) latanoprost patients reported ocular hyperemia as an adverse event ($P = .001$ for difference between latanoprost and bimatoprost). The mean onset day of reporting hyperemia was about 24 days for all treatments. A larger proportion of hyperemia adverse events was ongoing at the study end in the bimatoprost (67/110, 60.9%) and travoprost (53/90, 58.9%) groups than in patients treated with latanoprost (33/71, 46.5%). In all, 21/137 (15.3%) patients receiving bimatoprost, 14/138 (10.1%) patients treated with travoprost, and 8/136 (5.9%) latanoprost-treated patients reported moderate hyperemia. In addition, 4/137 (2.9%) patients in the bimatoprost group, 3/138 (2.2%) receiving travoprost, and 1/136 (0.7%) receiving latanoprost reported severe hyperemia. One patient in the travoprost group discontinued from the study owing to a persistent "red eye" problem; one bimatoprost-treated patient discontinued because of multiple ocular adverse events, and another discontinued the drug at the end of treatment because of ocular hyperemia.

Masked investigators' assessments of hyperemia were similar across treatments at baseline ($P = .827$) (Figure 9). Average hyperemia scores were significantly different among groups at both week 2 ($P = .005$) and week 12 ($P = .005$), however. At weeks 2 and 12, average hyperemia scores were lower for latanoprost-treated than for bimatoprost-treated patients ($P = .001$ for both visits). Hyperemia consistently was rated lowest in latanoprost-treated patients and highest in bimatoprost-treated patients, with those in the travoprost group receiving intermediate average ratings. Throughout the 12 weeks of treatment, the degree of hyperemia associated with each medication remained consistent.

At baseline, 5% to 7% of the patients in each treatment group reported eye redness when specifically asked about this symptom by the investigator (latanoprost, 9/136; bimatoprost, 10/137; travoprost, 7/138; $P = .739$). An increasing number of patients reported redness over time in all treatment groups. At week 12, the largest proportion of patients reporting redness was found in the bimatoprost group (46/132, 34.8%) followed by the travoprost and

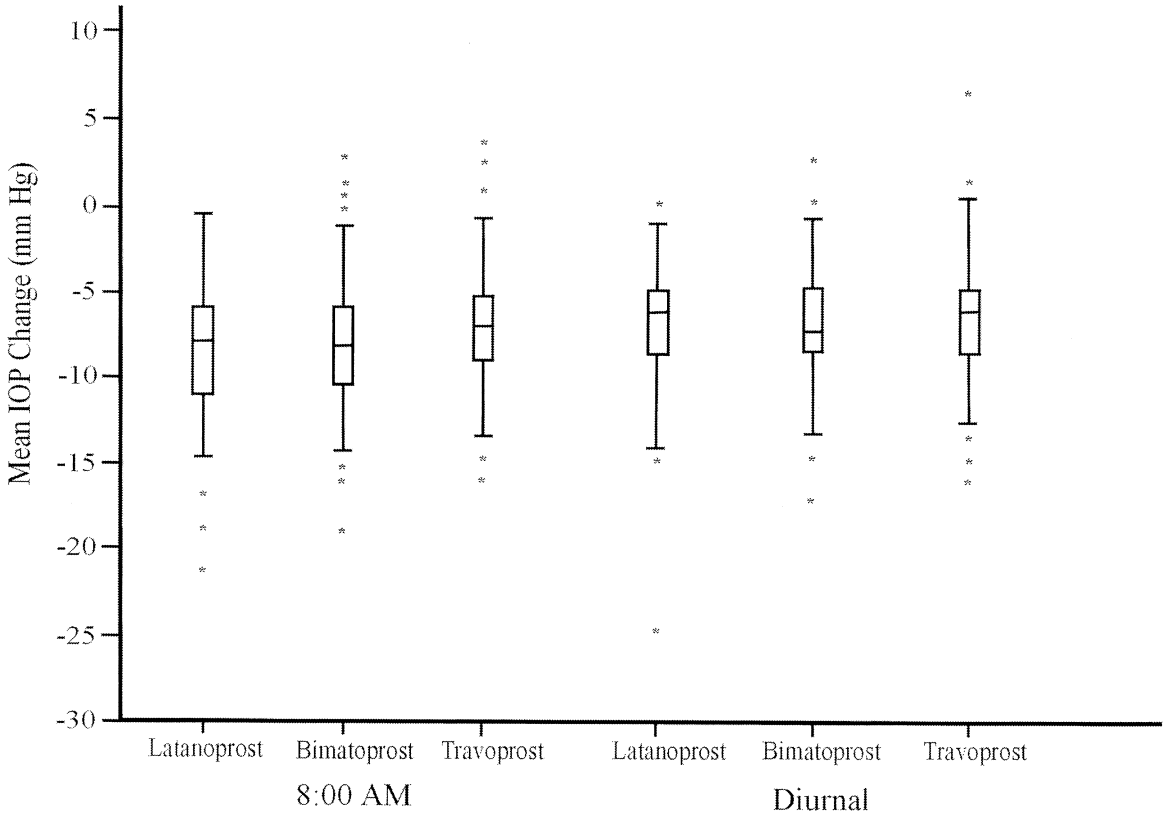

FIGURE 7. Distributions of reductions from baseline to week 12 in 8:00 AM and diurnal mean intraocular pressure (IOP) levels by treatment (intent-to-treat population). The bottom and top edges of the box are the 25th and 75th percentiles, and the center horizontal line is the median. The central vertical lines cover about 99% of the data range, and outliers are indicated by an asterisk.

latanoprost groups (36/132, 27.3%; and 21/131, 16.0%, respectively). Compared with bimatoprost-treated patients, fewer of those receiving latanoprost reported redness at any postbaseline visit ($P \leq .01$). In addition, fewer patients treated with latanoprost reported redness at weeks 2 and 12 than did those treated with travoprost ($P = .010$ and $P = .027$, respectively).

Overall, 23/136 (16.9%) latanoprost patients, 25/137 (18.2%) bimatoprost patients, and 23/138 (16.7%) travoprost patients reported systemic adverse events. Events reported by >2% of patients in any treatment group were nasopharyngitis, upper respiratory tract infection, and headache. Systemic events considered to be related to study medication were infrequent in any treatment group. Five patients (latanoprost, n = 3; bimatoprost, n = 1; travoprost, n = 1) reported a serious systemic adverse event, none of which was considered related to study medication. One patient with renal insufficiency died of acute renal failure.

DISCUSSION

WE BELIEVE THAT THIS IS THE FIRST RANDOMIZED, CONtrolled trial simultaneously comparing the IOP-lowering efficacy and safety of latanoprost, bimatoprost, and travoprost. Over 12 weeks, we found no significant differences in efficacy among the three medications in patients with open-angle glaucoma or ocular hypertension using an ITT analysis; results were supported by findings of per-protocol analyses. At the conclusion of the study, IOP measurements were significantly reduced from baseline for all three study groups at 8:00 AM, the primary efficacy variable, and neither the magnitude nor the distribution of the IOP reduction was statistically different among the three treatments. The 8:00 AM determination was chosen prospectively as the endpoint as it approximates the time of maximal IOP reduction by the three drugs[13,21,22,25–28] and the time of enhanced probability of pressure peaks based on circadian IOP patterns in studies of patients with glaucoma.[29,30] Blunting pressure peaks is a goal of glaucoma therapy as large diurnal fluctuations in IOP are an independent risk factor for the progression of disease.[31] In addition, no significant difference in the persistence of pressure lowering was detected across treatments as measured by change in mean IOP levels at week 12 at any individual time point or for the diurnal mean.

We also compared simultaneously the ocular tolerability and systemic adverse events of latanoprost, bimatoprost, and travoprost based on masked-investigator grading and

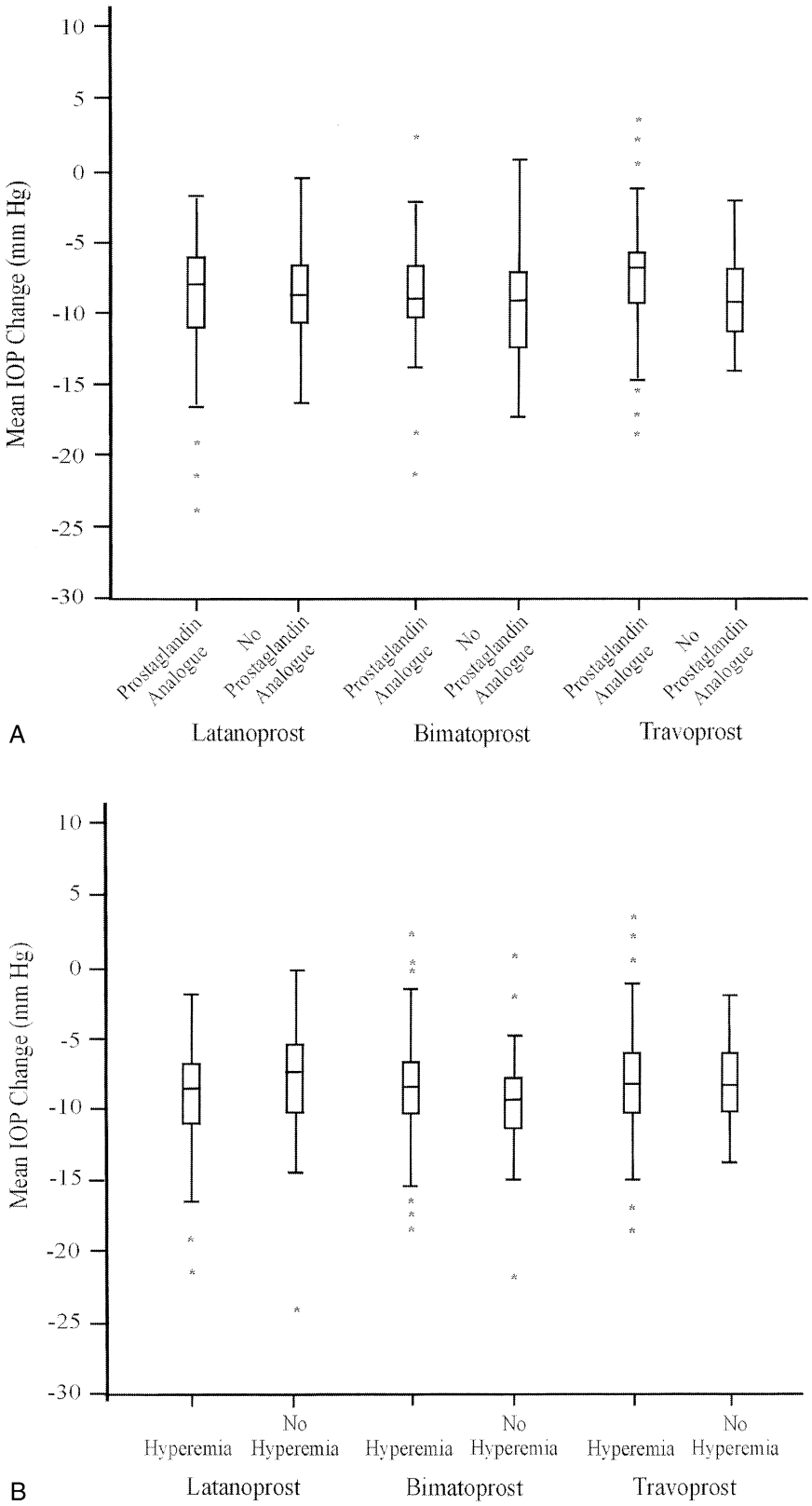

FIGURE 8. (A) Distributions of reductions from baseline to week 12 in 8:00 AM mean intraocular pressure (IOP) levels by treatment and prostaglandin analogue therapy at screening (intent-to-treat population). (B) Distributions of reductions from baseline to week 12 in 8:00 AM mean intraocular pressure (IOP) levels by treatment and occurrence of hyperemia (investigators' reports) (intent-to-treat population). The bottom and top edges of the box are the 25th and 75th percentiles, and the center horizontal line is the median. The central vertical lines cover about 99% of the data range, and outliers are indicated by an asterisk.

TABLE 3. Frequencies of Adverse Events (Safety Population)

	Latanoprost (n = 136)			Bimatoprost (n = 137)			Travoprost (n = 138)			
	n	%	No. of Events	n	%	No. of Events	n	%	No. of Events	*P* Value
Patients with at least one adverse event	87	64.0	137	104	75.9	200	95	68.8	159	.098
Patients with ocular adverse events	73	53.7	110	101	73.7	162	89	64.5	129	.003
Patients with systemic adverse events	23	16.9	27	25	18.2	38	23	16.7	30	.933
Patients with adverse events related to study medications	70	51.5	90	94	68.6	140	81	58.7	108	.015

TABLE 4. Ocular Adverse Events Reported by More Than 2% of Patients in Any Treatment Group: All Randomized Patients (Safety Population)

	Latanoprost (n = 136)			Bimatoprost (n = 137)			Travoprost (n = 138)		
	n	%	No. of Events	n	%	No. of Events	n	%	No. of Events
Ocular hyperemia/red eye	64	47.1	71	94	68.6	110	80	58.0	90
Eye irritation	9	6.6	10	15	10.9	16	6	4.3	6
Vision blurred	0		0	5	3.6	5	2	1.4	2
Eye pain	2	1.5	2	1	0.7	1	4	2.9	4
Growth of lashes	0		0	4	2.9	4	1	0.7	1
Skin discoloration	2	1.5	2	4	2.9	4	4	2.9	4
Dry eye (not elsewhere classified)	2	1.5	2	3	2.2	3	2	1.4	2
Visual acuity reduced	2	1.5	2	2	1.5	3	3	2.2	3
Pruritus	0		0	0		0	3	2.2	3

patient-generated self-reports. Patient reports of ocular adverse events, specifically eye redness, which constituted the most common ocular adverse event, were consistent with gradings of ocular hyperemia by masked investigators. In this study, significantly fewer latanoprost-treated patients reported eye redness. The intensity of ocular hyperemia also was greater in the bimatoprost and travoprost groups compared with the latanoprost group. All three drugs were well tolerated systemically.

The equivalent ocular hypotensive effects of latanoprost, bimatoprost, and travoprost in this study are consistent with most previous reports.[14,21,22] Two previous comparisons of bimatoprost to latanoprost[21,22] also revealed no significant difference in mean IOP reduction from baseline at 8:00 AM. An interpretation of data reported by Gandolfi and associates,[22] which suggested superior efficacy of bimatoprost compared to latanoprost at two other time points, noon and 4:00 PM after 3 months on treatment, was based on a post hoc analysis that did not take into account confounding differences in baseline IOP between the two treatment groups at just those two time points and that equaled the apparent greater efficacy.[32] Because a direct correlation between baseline IOP and IOP reduction in response to topical glaucoma treatment has been reported,[33] the use of unadjusted comparisons was not valid.

In another study comparing bimatoprost to latanoprost, DuBiner and colleagues,[21] in a 30-day trial, determined that the proportions of patients who reached target IOP levels were not different between those treated with latanoprost or bimatoprost. The significantly better diurnal IOP control reported for bimatoprost on day 29 again was confounded by differences in baseline IOPs at some times of day, and the efficacy did not differ when computed on a change in IOP basis.[32] In a 12-month comparison of latanoprost to travoprost, Netland and coworkers[14] found that mean IOP levels were statistically similar between treatment groups after the week 2 visit, except for a small, statistically significantly greater mean reduction with travoprost in the 4:00 PM values when pooled across visits. Post hoc subset analyses are subject to possible bias and an FDA review of that study concluded that "the IOP lowering ability of AL-6221 [travoprost] 0.004% is not superior to Xalatan [latanoprost] 0.005% by a clinically significant amount."[34] In the present study, we found no evidence for a greater persistence of pressure lowering in the afternoon by travoprost compared to latanoprost.

The single exception to reports of equality of efficacy for the three potent prostaglandin analogues was a recent 6-month study by Noecker and co-workers.[23] They reported significantly greater mean IOP reductions for bimatoprost compared to latanoprost; however, the investigators did not

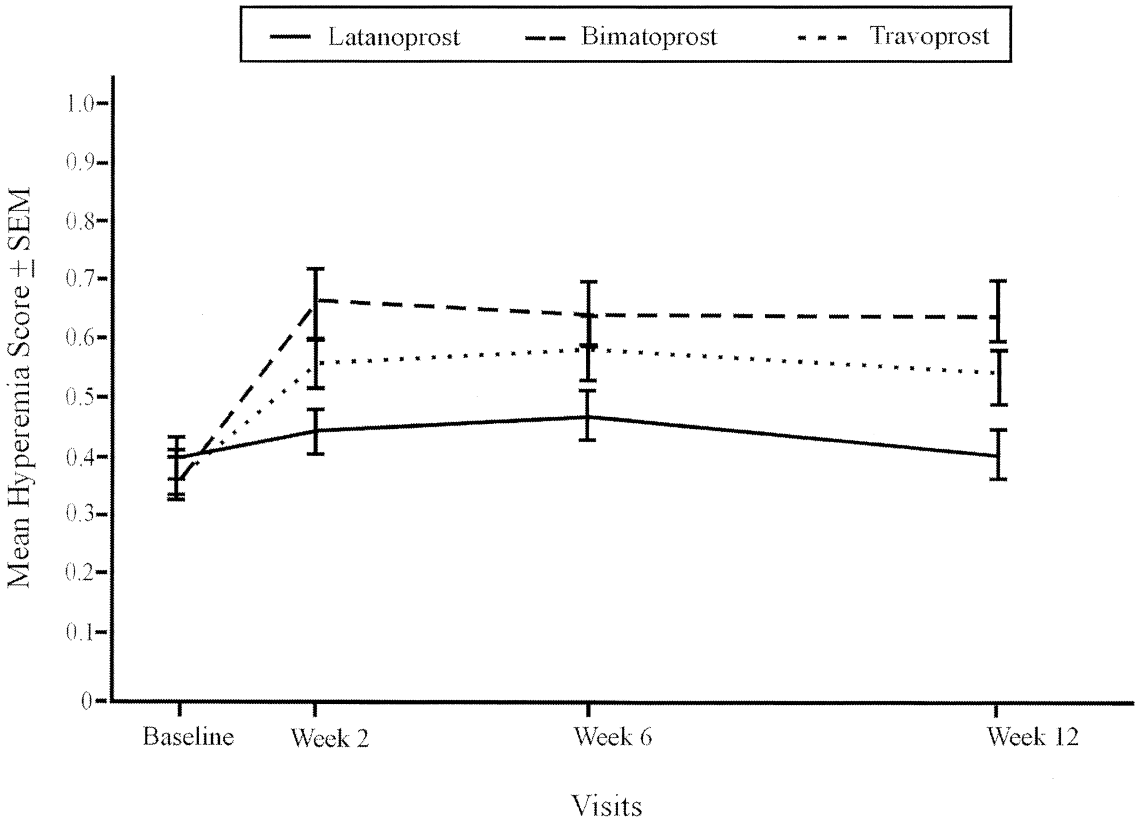

FIGURE 9. Mean hyperemia (investigators' assessments) score by treatment and visit.

TABLE 5. Intraocular Pressure-Lowering Effectiveness of Latanoprost and Bimatoprost Administered Once Daily in the Evening*

Reference	Study Duration	Randomized to Drug (n)	Mean Baseline AM IOP (mm Hg), Time	Mean Change in AM IOP (mm Hg)	% Reduction in AM IOP
Latanoprost†					
Alm et al.,[10] 1995	6 months	89	*25.5** 8:00 AM	*−8.7*	*34.1*
Camras et al.,[11] 1996	6 months	128	*25.6* 8:00 AM	*−7.2*	*28.1*
Watson et al.,[12] 1996	6 months	149	26.2 9:00 AM	−9.1	34.7
Gandolfi et al., [22] 2001	3 months	113	25.7 8:00 AM	*−7.8*	*30.4*
Noecker et al.,[23] 2003	6 months	136	24.9 8:00 AM	*−6.0*	*24.1*
Parrish et al., 2003 (Present study)	3 months	136	25.7 8:00 AM	−8.6	33.5
Bimatoprost					
Brandt et al.,[25] 2001	3 months	234	*26.1* 8:00 AM	−9.2	35.2
Sherwood et al.,[13] 2001	6 months	474	*24.6* 10:00 AM	−8.1	32.9
Gandolfi et al.,[22] 2001	3 months	119	25.7 8:00 AM	*−8.1*	*31.5*
Noecker et al.,[23] 2003	6 months	133	25.0 8:00 AM	*−7.5*	*30.0*
Parrish et al., 2003 (Present study)	3 months	136	25.7 8:00 AM	−8.7	33.9

*Numbers in italics indicate estimates derived from published line graphs or bar charts for studies that did not provide raw data.
†Patients received latanoprost in the morning during the first 3 months and in the evening during the final 3 months of the study.

adjust for significant differences in the noon baseline IOP level and did not report standard deviations or 95% confidence limits for estimates of differences in IOP reductions after baseline. Without this information, it is not possible to compare fully their results to ours. However, one can say that the Noecker et al.[23] study results differ remarkably from the results of this study and all previous literature in this field (Table 5) in two respects. First, in the study by Noecker and colleagues, the mean pressure-lowering effect of latanoprost at 8:00 AM (24.1%) was substantially less than that reported in

the present study (33.5%), the Gandolfi[22] study (30.4%), and in three other large published studies in similar patients,[10–12] and with the expected efficacy noted by Stjernschantz during the development of latanoprost.[35,36] Second, the percentage of poor responders to latanoprost in the Noecker study was far higher than in our study or in any previous study. Conversely, the response to bimatoprost in the Noecker study was consistent with findings of our report and other reports (Table 5).[13,22,25]

In an effort to find a possible explanation for the different results of the present study and the Noecker study,[23] we postulated two ways in which the results of such studies might reflect patient selection bias or measurement bias.

First, we postulated that patients referred to such studies might be biased on the basis of previous good or poor response to one of the prostaglandin analogues. It is notable that many patients in our study and in the study by Noecker and colleagues[23] previously had been treated with prostaglandin analogues, primarily with latanoprost. We therefore performed a subgroup analysis, and in Figure 8A we present box plots for the mean pressure change at 8:00 AM at week 12 for each of the three drugs for the subsets that had or had not been treated previously with a prostaglandin analogue. No statistically significant differences were noted, and there was not even a trend for those previously treated to be more responsive than those not previously treated. It is therefore clear that the present study did not include an unrepresentative sample of super-responders to latanoprost.

Our second postulate was that the masking of patients might have been broken by the presence of hyperemia, potentially leading to a biased measurement of IOP. Hyperemia has been shown previously to occur with higher frequency in patients treated with either bimatoprost or travoprost compared to latanoprost.[14,22] In Figure 8B, we present box plots for the mean IOP change at 8:00 AM at week 12 for those patients in whom hyperemia was ever or never recorded by the investigator. There was no significant difference or even a trend to finding lower IOP levels in patients without hyperemia, suggesting that such a bias was not a factor in the results of this study.

It is not clear why latanoprost-treated patients had a poorer response in the study by Noecker et al.[23] compared to the present study, the Gandolfi[22] and DuBiner[21] studies, and the other previous studies of latanoprost cited in Table 5.[10–12] However, subgroup analyses based on either prior prostaglandin use or presence of hyperemia were not performed by Noecker et al.[23]

This study confirms the findings of previous comparative studies that have evaluated hyperemia after the use of these three topical prostaglandin analogues.[14,22,23] Hyperemia rates in patients treated with latanoprost have been found to be less than half those for bimatoprost-treated patients after 3 and 6 months of therapy, and hyperemia has been shown to be less severe in those receiving latanoprost vs bimatoprost.[22,23] Latanoprost also has been associated with lower hyperemia rates than travoprost.[14] In an independent study in healthy patients, Stewart and co-workers[37] demonstrated that latanoprost causes significantly less short-term hyperemia than either bimatoprost or travoprost. The patient-initiated discontinuation of topical treatment was not different among the three groups in our study; nevertheless, the brief nature of the investigation precludes drawing conclusions regarding long-term patient acceptability.

In conclusion, this 12-week study demonstrates that latanoprost, bimatoprost, and travoprost are equally potent IOP-lowering treatments that are generally well tolerated systemically. Significantly fewer patients reported symptoms of ocular hyperemia with latanoprost treatment.

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APPENDIX

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