A Six-month Randomized Clinical Trial Comparing the Intraocular Pressure-lowering Efficacy of Bimatoprost and Latanoprost in Patients With Ocular Hypertension or Glaucoma

ROBERT S. NOECKER, MD, MONTE S. DIRKS, MD, NEIL T. CHOPLIN, MD, PAULA BERNSTEIN, MS, AMY L. BATOOSINGH, AND SCOTT M. WHITCUP, MD, FOR THE BIMATOPROST/LATANOPROST STUDY GROUP

• PURPOSE: To compare the intraocular pressure (IOP)-lowering efficacy and safety of topical bimatoprost 0.03% with latanoprost 0.005%.

• DESIGN: Multicenter, randomized, investigator-masked clinical trial.

• METHODS: After washout of glaucoma medications, ocular hypertension or glaucoma patients were randomly assigned to once-daily bimatoprost 0.03% (n = 133) or latanoprost 0.005% (n = 136) for 6 months. The primary outcome measure was mean change from baseline IOP (8 AM, 12 PM, 4 PM). Secondary measures included mean IOP, ophthalmologic examination, adverse events, and the percentage of patients reaching specific target IOPs.

• RESULTS: Mean change from baseline IOP was significantly greater for bimatoprost patients than for latanoprost patients at all measurements on each study visit; 1.5 mm Hg greater at 8 AM ($P < .001$), 2.2 mm Hg greater at 12 PM ($P < .001$), and 1.2 mm Hg greater at 4 PM ($P = .004$) at month 6. At the end of the study, the percentage of patients achieving a ≥20% IOP decrease was 69% to 82% with bimatoprost and 50% to 62% with latanoprost ($P \leq .003$). In addition, the distribution of patients achieving target pressures in each range (≤13 to ≤ 15 mm Hg, >15 to ≤ 18 mm Hg, and > 18 mm Hg) showed that bimatoprost produced lower target pressures compared with latanoprost at all times measured ($P \leq .026$). Few patients were discontinued for adverse events (6 on bimatoprost; 5 on latanoprost). On ophthalmologic examination, conjunctival hyperemia ($P < .001$) and eyelash growth ($P = .064$) were more common in bimatoprost patients.

• CONCLUSIONS: Bimatoprost is more effective than latanoprost in lowering IOP. Both drugs were well tolerated, with few discontinuations for adverse events. (Am J Ophthalmol 2003;135:55–63. © 2003 by Elsevier Science Inc. All rights reserved.)

GLAUCOMA IS AN OPTIC NEUROPATHY ASSOCIATED with retinal ganglion cell death that results in visual field loss. Elevated intraocular pressure (IOP) is a primary risk factor for the disease and a prime target for therapy. Recently, a large, randomized clinical trial demonstrated that the risk of progression of glaucomatous visual field loss is reduced at lower IOPs.[1] In addition, results from the Ocular Hypertension Treatment Study[2] showed that a 20% IOP reduction from baseline decreased the risk of developing optic disk cupping and/or visual field loss in ocular hypertensive patients from 9.5% to 4.4%.

Both the prostamide bimatoprost and the prostaglandin latanoprost have been shown to be effective IOP-lowering agents in double-masked clinical comparisons with timolol.[3–7] Two short-term, randomized, clinical comparisons of bimatoprost and latanoprost suggest, however, that bimatoprost provides better IOP control than latanoprost.[8,9]

The purpose of the present study was to compare the IOP-lowering efficacy and safety of bimatoprost and la-

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From the University of Arizona (R.S.N.), Tucson, Arizona; the Black Hills Regional Eye Institute (M.S.D.), Rapid City, South Dakota; Eye Care of San Diego (N.T.C.), San Diego, California; and Allergan, Inc. (P.B., A.L.B., S.M.W.), Irvine, California.

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Inquiries to Scott M. Whitcup, MD, 2525 Dupont Dr, Irvine, CA 92612-1599; fax: (714) 246-6756; e-mail: whitcup_scott@allergan.com

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tanoprost in patients with ocular hypertension or glaucoma in a large cohort of patients followed for 6 months.

DESIGN

THIS STUDY WAS A MULTICENTER, PROSPECTIVE, RANDOMized, investigator-masked, parallel-group clinical comparison.

METHODS

THIS STUDY WAS CONDUCTED AT 18 CENTERS ACROSS THE United States. Investigators who participated in the study are listed in the Appendix. The protocol was in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki (1996) and in accordance with applicable Institutional Review Board regulations (United States 21 Code of Federal Regulations [US 21 CFR] part 56.103). Study participants gave informed consent before initiation of any study-related procedures. The study was performed in compliance with informed consent regulations (US 21 CFR part 50).

Patients with a diagnosis of ocular hypertension or chronic glaucoma were eligible to participate in the study if they were at least 18 years of age, required IOP-lowering therapy for both eyes, and had best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity scores equivalent to a Snellen score of 20/100 or better in each eye. At a prestudy visit, IOP-lowering medications were discontinued. The washout period was 4 days for parasympathomimetics and carbonic anhydrase inhibitors, 2 weeks for sympathomimetics and α-agonists, 4 weeks for β-blockers, or 8 weeks for prostaglandins and prostamides. After the appropriate washout period, patients returned for the baseline visit. At baseline (day 0), IOPs had to be between 22 mm Hg and 34 mm Hg in each eye at time 0 (approximately 8 AM) with asymmetry in IOP between the eyes of no more than 5 mm Hg. Patients were excluded from the study if they had substantial ocular irritation at baseline, had functionally significant or progressive visual field loss within the last year, had uncontrolled systemic disease, had unstable chronic therapy with agents that could affect IOP, required chronic use of other ocular medications, had intraocular surgery within the 3 months before baseline, or were pregnant.

On day 0 (baseline), patients who qualified for the study were randomly assigned, from a computer-generated randomization list of subject numbers, to receive either once-daily bimatoprost 0.03% (n = 133) or latanoprost 0.005% (n = 136). There were six scheduled visits: prestudy, day 0 (baseline), week 1, and months 1, 3, and 6. Patients were instructed to instill one drop of study medication in each eye in the evening (between 7 PM and 9 PM). To ensure masking, medication bottles were affixed with study labels giving identical patient instructions and the bottles were packaged in identical cartons. Because the bottles were slightly different in shape, the dispensing and collecting of study medications was performed by persons other than those collecting efficacy or safety data.

Before dispensing, latanoprost was stored under refrigeration at 36 F to 46 F (2 C to 8 C) in the masked study carton and bimatoprost was stored at room temperature in the masked study carton. Latanoprost was to be discarded 6 weeks after opening, so new bottles of study medication were dispensed to both treatment groups every month to ensure that patients were using medications within the latanoprost label-specified timeframe and to preserve masking. This required visits at months 2, 4, and 5 (just to receive study medication) in addition to the follow-up visits.

For primary outcome measures, mean change from baseline IOP was the primary efficacy variable. Intraocular pressure was measured using a Goldmann applanation tonometer mounted to a slit-lamp biomicroscope at approximately 8 AM, 12 PM and 4 PM at baseline, at week 1, and at months 1, 3, and 6. The times of day for each measurement were chosen because they are evenly spaced throughout the daylight hours and are commonly used in studies of this type. Intraocular pressure was measured at least twice in each eye, and if the difference between the first and second reading was greater than 2 mm Hg, a third reading was taken. Intraocular pressure was reported as either the mean of two readings or the median of three readings. Secondary outcome measures obtained at follow-up included mean IOP, the percentage of patients reaching specific target IOPs, and the percentage of patients achieving at least a 15% or 20% decrease in IOP from baseline (responder rate).

Secondary outcome measures also included safety information, including ophthalmologic examination and adverse events. An ophthalmologic examination including measurement of visual acuity and slit-lamp biomicroscopy was performed at each visit. Ophthalmoscopy was performed through a dilated pupil to assess the cup/disk ratio and posterior segment at the prestudy and month 6 visits after all other study-related procedures. Biomicroscopic and ophthalmoscopic findings were rated on a 5-point scale of severity (0 = none, 0.5 = trace, 1 = mild, 2 = moderate, 3 = severe). Adverse events were recorded at each study visit. Visual field examinations were performed at prestudy and at month 6 using an automated perimetry test. Visual fields were reported as normal or abnormal, and the mean deviation/mean defect/mean loss was recorded in decibels.

Efficacy analyses were conducted on an intent-to-treat basis, including all randomized patients, with last observation carried forward. For patients who discontinued the study and for missing data between visits, the last clinic visit or the visit before the missing visit was carried forward in the analyses. Similar results (not shown) were attained

when the analysis was performed on a per-protocol population without imputation for missing data. The statistical package used was SAS version 8.2. (SAS Institute, Cary, North Carolina, USA).

The primary analysis of efficacy was based on mean change from baseline in IOP. All analyses treated the patient as the experimental unit. All IOP results were based on the average from both eyes. The change from baseline in IOP was computed as the average of the IOP changes in both eyes.

As planned (n = 96 patients in each treatment group), the power of the study was 81% to claim noninferiority of bimatoprost to latanoprost, assuming a noninferiority margin of 1.75 mm Hg and common standard deviation of 4.25 mm Hg. A strategy of combined tests of noninferiority and superiority suggested by Morikawa and Yoshida[10] was employed for the between-group comparisons of mean IOP change from baseline and for mean IOP. Using this methodology, the test for noninferiority, based on confidence intervals, was conducted first. If the one-sided 95% confidence interval for the treatment effect (in this case the upper limit determined from bimatoprost minus latanoprost) was below the noninferiority margin and also below zero, then there was evidence of statistical significance at the 5% level. In this instance the *P* value associated with the test of superiority was calculated. If the superiority test resulted in a *P* value $\leq$ .05 then, by definition, the noninferiority criterion was met and only superiority test results were presented. Testing was accomplished by a two-way (treatments, centers) analysis of variance (ANOVA). Treatment group differences were declared statistically significant for $P \leq .05$. Estimated differences were based on the least-squares predicted means from the two-way ANOVA model.

If a treatment group difference in any parameter was statistically significant at baseline, an additional analysis was performed that incorporated baseline into the model as a covariate. In no instance did the significance of the treatment group differences change when the covariate-adjusted analysis was performed.

For other data, nominal categorical variables were analyzed using the Fisher exact test, Pearsons' χ^2 test, or Cochran–Mantel–Haenszel methods.[11] Ordinal categorical variables were analyzed with the Wilcoxon rank-sum test.[12] Continuous variables were analyzed using ANOVA. The analyses of the proportion of patients who achieved desirable target IOP levels and nonresponder rates were compared between groups using the Fisher exact test. In addition, treatment group comparisons considered the distribution of patients by IOP range ($\leq$15 mm Hg, >15 mm Hg and $\leq$18 mm Hg, and >18 mm Hg). The Cochran–Mantel–Haenszel test[11] with modified ridits using the row mean score statistic and stratification by site was used for these comparisons.

TABLE 1. Patient Disposition

	Bimatoprost	Latanoprost
Enrolled	133	136
Completed	124 (93.2%)	125 (91.9%)
Discontinued	9 (6.8%)	11 (8.1%)
Lack of efficacy	0 (0.0%)	1 (0.7%)
Adverse events*	6 (4.5%)	5 (3.7%)
Administrative reasons†	2 (1.5%)	2 (1.5%)
Protocol violations‡	1 (0.8%)	2 (1.5%)
Other	0 (0.0%)	1 (0.7%)

*In the bimatoprost group: allergic skin reaction, blepharoptosis, burning eye, conjunctival hyperemia, and eye pruritus; in the latanoprost group: allergic conjunctivitis, death, iritis, lung carcinoma, and pancreatitis.

†Lost to follow-up, relocated, or for personal reasons.

‡Improper entry or noncompliance.

RESULTS

A TOTAL OF 320 PATIENTS WERE SCREENED FOR POSSIBLE inclusion in the present study. Of these 320, 51 (19%) failed the inclusion/exclusion criteria and 269 were enrolled. The reasons patients were excluded from the study were failure to meet IOP criteria (26), noncompliance with or inability to meet schedule (7), withdrawal of consent at or before baseline visit (7), use of excluded medication (5), ophthalmic exclusion criteria (4), and unknown (2). Of the 269 enrolled patients, 249 (92.6%) completed the 6-month study period (Table 1). A similar percentage of patients in each treatment group discontinued the study early: 1 (latanoprost) for lack of efficacy; 11 (6, bimatoprost; 5, latanoprost) for adverse events; and 8 (3 bimatoprost; 5 latanoprost) for administrative reasons or protocol violations.

There were no statistically significant differences between the two treatment groups in patient demographics or baseline characteristics (Table 2). Patients ranged in age from 24 to 88 years (mean, 61.3). There were more women than men in the study. Most of the patients were Caucasian (83%; 222/269); 11% (29/269) were Black, and 6% (17/269) were Hispanic. The majority of patients were diagnosed with primary open-angle glaucoma (56%; 150/269). A greater percentage of patients in the latanoprost group had a history of pulmonary disease (4.4% vs 0.0%; $P = .030$), and a greater percentage of patients in the bimatoprost group were taking serum lipid-reducing agents (33.8% vs 19.1%; $P = .008$). The percentage of patients entering the study who underwent washout of other IOP-lowering agents was similar between treatment groups.

Baseline mean IOPs were similar between the treatment groups at 8 AM (25.0 $\pm$ 0.24 mm Hg for bimatoprost and 24.9 $\pm$ 0.23 mm Hg for latanoprost; $\pm$SEM) and 4 PM

TABLE 2. Demograpic and Baseline Characteristics of Patients

	Bimatoprost (n = 133)	Latanoprost (n = 136)	*P* Value
Age in years (mean ± SEM)	61.5 ± 1.0	61.0 ± 1.1	.725
Sex			.900
Male	50 (37.6%)	53 (39.0%)	
Female	83 (62.4%)	83 (61.0%)	
Race			.695*
Black	13 (9.8%)	16 (11.8%)	
Caucasian	112 (84.2%)	111 (81.6%)	
Hispanic	8 (6.0%)	9 (6.6%)	
Iris color			.393†
Brown	49 (36.8%)	52 (38.2%)	
Blue	36 (27.1%)	37 (27.2%)	
Hazel	20 (15.0%)	19 (14.0%)	
Dark brown	9 (6.8%)	15 (11.0%)	
Blue-gray	11 (8.3%)	4 (2.9%)	
Green-brown	2 (1.5%)	3 (2.2%)	
Green	2 (1.5%)	2 (1.5%)	
Blue/gray-brown	2 (1.5%)	1 (0.7%)	
Gray	1 (0.8%)	1 (0.7%)	
Other	1 (0.8%)	2 (1.5%)	
Diagnosis			
Primary open-angle glaucoma	72 (54.1%)	78 (57.4%)	.625
Other glaucoma‡	12 (9.0%)	9 (6.6%)	>.214
Ocular hypertension	46 (34.6%)	47 (34.6%)	>.999
Glaucoma/ocular hypertension (different eyes)	3 (2.3%)	2 (1.5%)	.682
Washout required			.370
Yes	91 (68.4%)	85 (62.5%)	
Apha-agonist	12 (9.0%)	11 (8.1%)	
Beta-blocker combination therapy	3 (2.3%)	4 (2.9%)	
Carbonic anhydrase inhibitors	26 (19.5%)	26 (19.1%)	
Nonselective beta-blockers	25 (18.8%)	40 (29.4%)	
Other medications	9 (6.8%)	7 (5.1%)	
Prostaglandins	38 (28.6%)	30 (22.1%)	
Selective beta-blocker	1 (0.8%)	1 (0.7%)	
Sympathomimetics/cholinergics	1 (0.8%)	2 (1.5%)	
No	42 (31.6%)	51 (37.5%)	

**P* value for black vs nonblack (Caucasian, Hispanic).

†*P* value for brown or dark brown vs light (blue, hazel, green, gray, blue-gray, green-brown, blue/gray-brown, blue-green, or right eye brown and left eye hazel).

‡Includes chronic angle-closure glaucoma pseudoexfoliative glaucoma, and pigmentary glaucoma in at least one eye. One patient in each group had primary open-angle glaucoma in one eye and chronic angle-closure glaucoma in the other.

(22.6 ± 0.28 mm Hg for bimatoprost and 22.5 ± 0.27 mm Hg for latanoprost). At 12 PM the baseline IOP for bimatoprost (24.0 ± 0.27 mm Hg) was significantly higher than that for latanoprost (23.3 ± 0.27 mm Hg; $P = .028$).

At all follow-up timepoints, bimatoprost achieved greater mean IOP decreases from baseline than did latanoprost (Figure 1). All of these differences met the criteria for statistical superiority, as defined in the statistical plan. At month 6, the mean decrease from baseline IOP was 1.5 mm Hg greater with bimatoprost than with latanoprost at 8 AM ($P < .001$), 2.2 mm Hg greater at 12 PM ($P < .001$), and 1.2 mm Hg greater at 4 PM ($P = .004$).

Bimatoprost achieved statistically significantly lower mean IOPs than latanoprost at all three measurements on all four follow-up visits (*P* values ranging from < .001 to .049). The diurnal measurements on the final study visit ranged from 16.5 to 17.4 mm Hg in the bimatoprost group and from 17.6 to 18.9 mm Hg in the latanoprost group ($P \leq .008$; Figure 2).

Responder rates were defined as the percentage of patients who achieved at least a 15% or 20% IOP decrease. At 6 months, the percentage of patients achieving at least a 15% decrease in IOP ranged (over 8 AM, 12 noon, and 4 PM) from 83% to 89% (110 to 118/133) in the bimatoprost

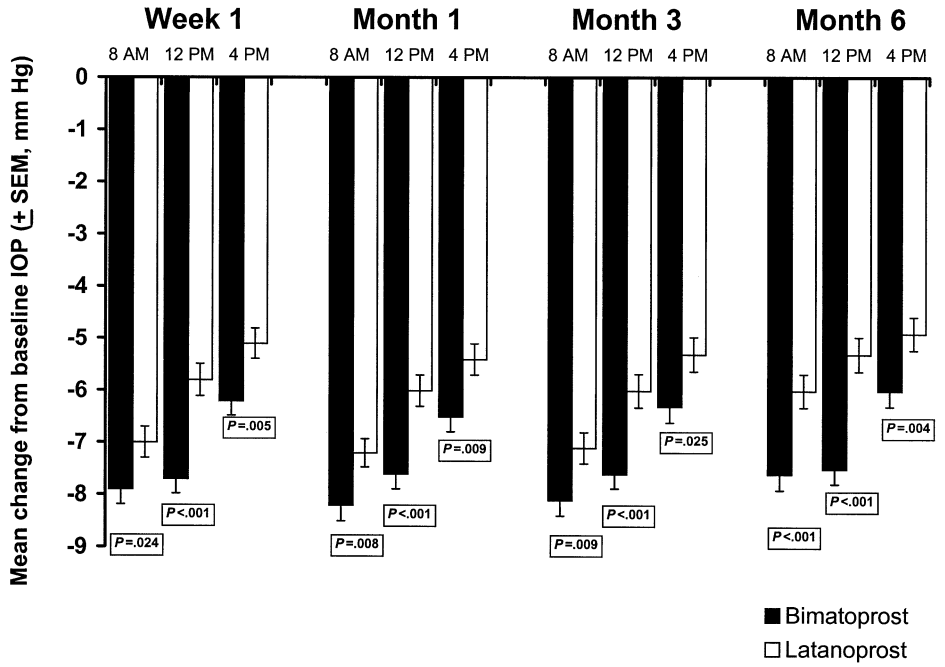

FIGURE 1. Mean (± standard error of the mean [SEM]) change from baseline intraocular pressure (IOP) for all 12 follow-up measurements. The mean IOP reduction from baseline was statistically significantly greater with bimatoprost than with latanoprost at each timepoint ($P \leq .024$). Solid bars = bimatoprost; open bars = latanoprost.

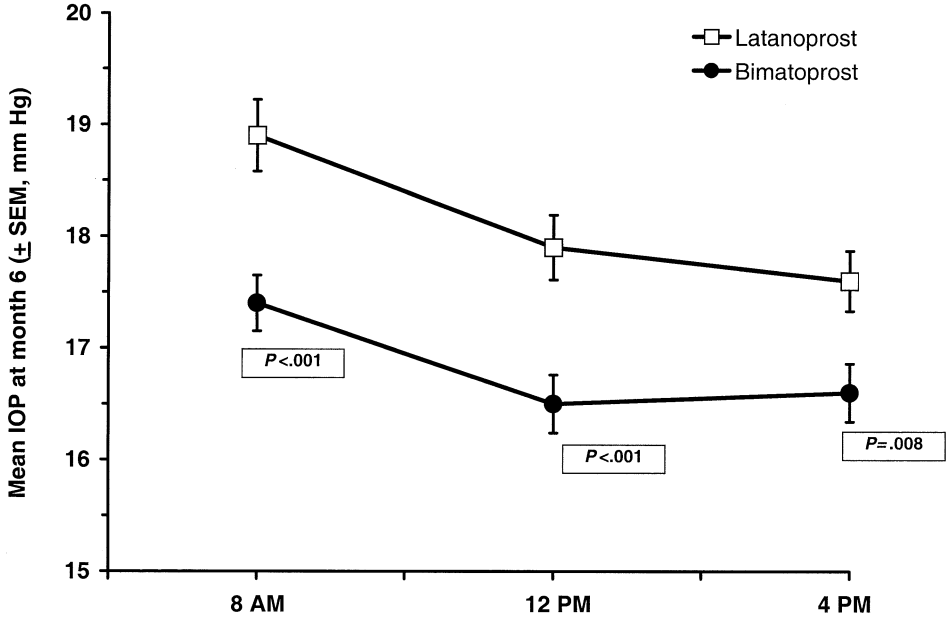

FIGURE 2. Diurnal mean (± standard error of the mean [SEM]) intraocular pressure (IOP) at the 6-month study visit. Open box = latanoprost; solid circle = bimatoprost.

group and from 65% to 72% (88 to 98/136) in the latanoprost group. The percentage of patients achieving at least a 20% decrease in IOP ranged from 69% to 82% (92 to 109/133) in the bimatoprost group and from 50% to 62% (68 to 85/136) in the latanoprost group (Table 3).

The distribution of patients achieving target pressures in each range (≤13 to ≤15 mm Hg, >15 to ≤18 mm Hg, and >18 mm Hg) showed that bimatoprost produced statistically significantly lower target pressures compared with latanoprost at each of the timepoints at month 6 (8 AM, $P = .014$; 12 PM, $P = .006$; 4 PM, $P = .026$). The percentage of patients achieving target pressures ranging from ≤13 mm Hg to ≤20 mm Hg was always greater with bimatoprost. Treatment group comparisons were also performed

TABLE 3. Responder Rates

	≥15% IOP Reduction			≥20% IOP Reduction		
	Bimatoprost (n = 133)	Latanoprost (n = 136)	*P* Value	Bimatoprost (n = 133)	Latanoprost (n = 136)	*P* Value
8 AM	89%	72%	.001	79%	62%	.003
12 PM	89%	70%	<.001	82%	61%	<.001
4 PM	83%	65%	.001	69%	50%	.002

IOP = intraocular pressure.

for each of the eight individual target pressures from ≤13 to ≤20 mm Hg, and the majority showed statistical significance (Figure 3).

The safety evaluation was based both on ophthalmologic examination and on reported adverse events. On slit-lamp biomicroscopy, conjunctival hyperemia was the most common finding with both medications, but occurred significantly more frequently in bimatoprost-treated patients ($P < .001$). Conjunctival hyperemia was noted on slit-lamp biomicroscopy in as many as 55.4% of patients treated with bimatoprost and as many as 42.5% of patients treated with latanoprost. Conjunctival hyperemia was mostly trace or mild with both medications, but the mean grades of hyperemia (scale of 0–3) were up to 0.27 units greater with bimatoprost than with latanoprost (0.55 vs 0.28). A categorical analysis showed that the differences in the distribution of severity grades was statistically significant; median severity scores were 0.5 (trace) for bimatoprost and 0.0 (none) for latanoprost ($P < .001$). Eyelash growth was noted on biomicroscopy in six patients receiving bimatoprost and in one patient receiving latanoprost ($P = .064$). Corneal findings were equivalent in patients treated with bimatoprost or latanoprost. Anterior uveitis occurred in one patient in the latanoprost group and required treatment with topical corticosteroids; it did not occur in any patients treated with bimatoprost. There was one report of increased iris pigmentation in a patient treated with bimatoprost. There were no cases of cystoid macular edema in either group.

There was no statistically significant difference in change in visual acuity between the two treatment groups: 94.6% of patients on bimatoprost and 94.1% of patients on latanoprost had stable or improved visual acuity. There was little change in cup-to-disk ratios during the course of the study with either medication. An increase in cup-to-disk ratio was reported in two of 129 (1.6%) patients treated with bimatoprost and five of 133 (3.8%) patients treated with latanoprost ($P = .485$). There was no statistically significant difference in visual fields between the two treatment groups either at prestudy (bimatoprost: −1.830 dB; latanoprost: −2.218 dB; $P = .536$) or at the end of the study (bimatoprost: 0.957 dB; latanoprost: 1.244 dB; $P = .877$).

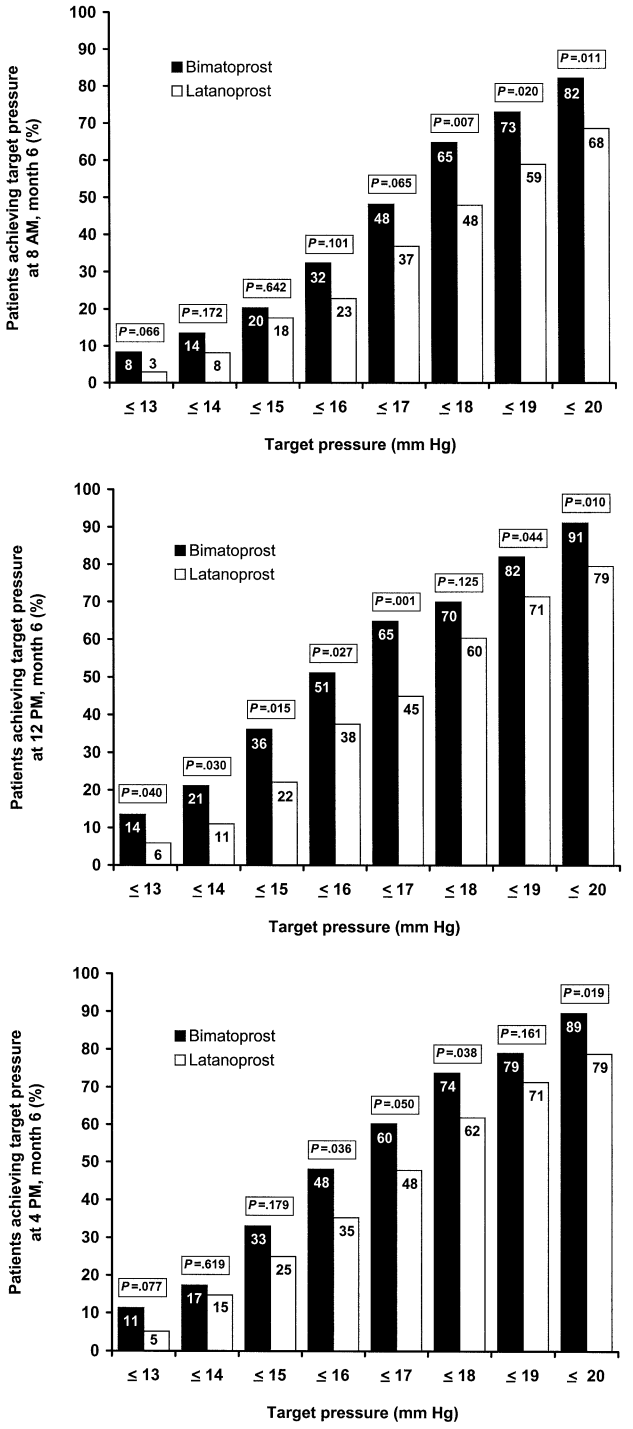

FIGURE 3. Percentage of patients achieving target intraocular pressure (IOP) at month 6. (Top) 8 AM. (Middle) 12 PM. (Bottom) 4 PM. *P* values in the graph represent between-group comparisons. Target pressure values were also calculated based on the distribution of patients with IOP ≤15 mm Hg, IOP from >15 to ≤18 mm Hg, and IOP >18 mm Hg. This analysis showed a statistically significant difference between treatment groups at 8 AM ($P = .014$), 12 PM ($P = .006$), and 4 PM ($P = .026$). Solid bars = bimatoprost; open bars = latanoprost.

Discontinuations from study medication due to adverse events were uncommon and were similar between the two treatment groups: six of 133 (4.5%) for patients treated with bimatoprost and five of 136 (3.7%) for patients treated with latanoprost. Table 4 lists all adverse events that were reported in more than 5% of patients. No other adverse events showed a statistically significant between-group difference in incidence ($P \geq .119$). Conjunctival hyperemia, eyelash growth, and itching were significantly more common in patients treated with bimatoprost than with latanoprost ($P \leq .025$). Ocular burning was similar in the two treatment groups: 5.9% of patients treated with latanoprost and 5.3% of patients treated with bimatoprost. Twelve serious adverse events were reported in the study: eight with latanoprost and four with bimatoprost ($P = .377$). One death due to myocardial infarction occurred during the study in a patient receiving latanoprost. None of the 12 serious adverse events was reported to be related to the study medication.

TABLE 4. Adverse Events Reported for More Than 5% of Patients in Either Treatment Group

	Bimatoprost (n = 133)	Latanoprost (n = 136)	*P* Value
Conjunctival hyperemia	59 (44.4%)	28 (20.6%)	<.001
Eyelash growth	14 (10.5%)	0 (0.0%)	<.001
Ocular pruritus	13 (9.8%)	4 (2.9%)	.025
Ocular burning	7 (5.3%)	8 (5.9%)	>.999

DISCUSSION

BIMATOPROST LOWERED IOP SIGNIFICANTLY MORE THAN did latanoprost at all timepoints throughout the 6 months of this study. In any clinical trial, the study conclusion should be based primarily on the prospectively determined primary outcome measure. At every measurement throughout the study, mean changes from baseline IOP (primary outcome measure) were significantly greater with bimatoprost than they were with latanoprost ($P \leq .025$). By the end of the study, mean changes from baseline were 1.2 to 2.2 mm Hg greater with bimatoprost than with latanoprost ($P \leq .004$). Moreover, the greater IOP-lowering efficacy of bimatoprost relative to latanoprost was also confirmed by the analysis of the mean IOP measurement, which showed that mean IOPs in the bimatoprost group were statistically significantly lower at all timepoints on all follow-up visits.

It is also important to assess the clinical relevance of the differences observed between the treatment groups in a clinical trial. The clinical significance of the greater IOP lowering achieved with bimatoprost can be illustrated by an analysis of the number of patients reaching specific target pressures. Clinicians frequently define a desired IOP range as a goal of glaucoma therapy.[13] Recent data from several studies show the clinical relevance of patients achieving specific low target pressures. In the Advanced Glaucoma Intervention Study (AGIS),[1] glaucoma patients with IOPs consistently below 18 mm Hg had no discernible additional visual field loss over a 6-year follow-up period. Similarly, a study by Mao and associates[14] found that all eyes with a mean IOP of ≤16 mm Hg remained stable, whereas eyes with higher IOPs showed an increasing risk of disease progression. At the end of the present study, more patients achieved low target pressures at all times of the day in the bimatoprost group than the in latanoprost group (Figure 3). Intraocular pressures ≤20 mm Hg were achieved in 82.0% to 91.0% of patients treated with bimatoprost compared with 68.4% to 79.4% of patients treated with latanoprost. Intraocular pressures ≤15 mm Hg were achieved by 20.3% to 36.1% of patients treated with bimatoprost compared with 17.6% to 25.0% of patients treated with latanoprost. When considered in the context of the earlier publications on the importance of low IOP, the target pressure analysis in the present study suggests that bimatoprost may reduce the risk of disease progression in more glaucoma and ocular hypertension patients than does latanoprost.

The clinical significance of the greater IOP-lowering efficacy of bimatoprost over latanoprost can also be assessed by analyzing the percentage of patients achieving a clinically meaningful decrease in IOP: a so-called responder analysis. Although there is not a complete consensus on the definition of a clinical responder, a decrease in IOP of 15% to 20% from baseline is frequently used to define a clinically relevant response to a glaucoma medication.[15–17] In the present study, the responder rate at 6 months was statistically significantly higher in the bimatoprost group than the latanoprost group at all times measured, regardless of whether a therapeutically relevant response was defined as a 15% or 20% IOP decrease (Table 3). Conversely, the nonresponder rate can be seen to be approximately twofold to threefold greater for patients receiving latanoprost. From a practical standpoint, these patients will require additional office visits to have their therapy changed, but more importantly, a delay in IOP lowering could place them at higher risk for optic nerve damage. Both greater IOP-lowering efficacy and an increased percentage of patients who respond to medication may explain the lower IOPs achieved with bimatoprost compared with latanoprost.

In this study, a number of precautions were taken to preserve masking. To ensure ideal stability of both medications, latanoprost and bimatoprost were kept in the original marketed containers and latanoprost was refrigerated before dispensing, as specified in the product labeling. Medication bottles were affixed with identical-appearing coded study labels and placed in masked cartons. In

addition, persons collecting efficacy and safety data were different from those administering, dispensing, and collecting the study medications. Finally, it is important to determine if previous exposure to either of the study medications affected the results. No patients had bimatroprost as their washout medication. Patients whose washout medication was latanoprost were distributed approximately equally between the treatment groups and the results of a subgroup analysis without these patients were similar to those based on all patients. Statistically, a test for significant interaction between treatment effect and washout medication (latanoprost or bimatoprost vs other medications) was performed using a two-way ANOVA model. Of the 12 postbaseline timepoints analyzed, 11 timepoints had P values $\geq .172$ while the other P value was .057. Based on these results, it is concluded that there was no significant interaction of latanoprost washout and treatment effect.

Both latanoprost and bimatoprost were well tolerated with very few discontinuations for adverse effects. Conjunctival hyperemia was the most common side effect for both medications. However, it was reported as an adverse event significantly more often in patients receiving bimatoprost than in patients receiving latanoprost and the mean grades of hyperemia were as much as 0.27 unit greater with bimatoprost than with latanoprost. Hyperemia with either medication did not appear to be associated with intraocular inflammation. Only one case of uveitis was noted in a patient receiving latanoprost. Eyelash growth and ocular pruritus were also significantly more common for patients treated with bimatoprost. There were no other significant differences in side effects between the two medications. The safety profiles seen in the present study were comparable to those seen in previously published clinical trials for both drugs.[3–9]

In conclusion, the IOP-lowering efficacy was greater with bimatoprost than with latanoprost as assessed by the primary efficacy measure (mean change from baseline IOP). Furthermore, the greater IOP-lowering efficacy seen with bimatoprost was confirmed by all of the secondary efficacy measures, including mean IOP and the percentage of patients reaching specific target pressures. More bimatoprost patients than latanoprost patients achieved at least a 15% or 20% reduction in IOP, which was statistically significant. On ophthalmic examination, conjunctival hyperemia and eyelash growth occurred significantly more frequently with bimatoprost; discontinuations for side effects, however, were low and equivalent for the two medications.

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THE BIMATOPROST/LATANOPROST STUDY GROUP

RICHARD S. BENNION, MD, WENATCHEE VALLEY CLINIC, Wenatchee, WA; Leonard Cacioppo, MD, Hernando Eye Institute, Brooksville, FL; Neil Choplin, MD, Eye Care of San Diego, San Diego, CA; Andrew Dannemann, MD, Eye Center South, Dothan, AL; Monte S. Dirks, MD, Black Hills Regional Eye Institute, Rapid City, SD; Harvey B. DuBiner, MD, Clayton Eye Center, Morrow, GA; Christopher Girkin, MD, University of Alabama at Birmingham School of Medicine, Callahan Eye Foundation Hospital, Birmingham, AL; David Godfrey, MD, Glaucoma Associates of Texas, Dallas, TX; Donald L. Kellum, MD, Boulder Medical Center, Boulder, CO; Dennis Kilpatrick, MD, Radiant Research, Scottsdale, AZ; Richard Lewis, MD, Grutzmacher and Lewis, Sacramento, CA; Charles McMahon, MD, St. Luke's Eye Care Center; Colorado Springs, CO; Robert J. Noecker, MD, University of Arizona, Department of Ophthalmology, Tucson, AZ; Stacey Pittman, MPM, Pittman Consulting, San Diego, CA; Mark S. Rubin, MD, International Eye Associates P.A., Ormond Beach, FL; Lisa P. Simpson, BS, Allergan Inc., Irvine, CA; Lloyd E. Suter, MD, Twin Tiers Eye Care Associates, Binghamton, NY; Celso Tello, MD, New York Eye and Ear Infirmary, Glaucoma Associates of New York, NY, NY; Michael Tepedino, MD, Cornerstone Eye Care, High Point, NC; Amanda M. VanDenburgh, PhD, Allergan Inc., Irvine, CA; and Jeffrey Whitsett, MD, Houston, TX.