

# Latanoprost, a Prostaglandin Analog, for Glaucoma Therapy

## Efficacy and Safety after 1 Year of Treatment in 198 Patients

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**Purpose:** To determine efficacy and safety of latanoprost, a prostaglandin analog for glaucoma, during 1 year of treatment.

**Methods:** After baseline measurements, 0.005% latanoprost was topically applied once daily for 12 months in patients from Scandinavia, the United Kingdom, and the United States who had elevated intraocular pressure (IOP). Diagnoses included ocular hypertension, chronic open-angle glaucoma, exfoliation syndrome, and pigment dispersion syndrome. Treatment was masked for the first 6 months and open-label during the second 6 months.

**Results:** Of the 272 patients initially enrolled, withdrawals were due to inadequate IOP control (1%), increased iris pigmentation (5%), other ocular problems (3%), systemic medical problems (3%), and nonmedical reasons (14%). Latanoprost significantly ( $P < 0.0001$ ) reduced diurnal IOP from  $25.3 \pm 3.0$  mmHg (mean  $\pm$  standard deviation) at baseline to  $17.4 \pm 2.7$  mmHg (32% reduction) at 12 months in the 198 patients who completed 1 year of treatment. The IOP reduction was maintained at a consistent level throughout the 12 months without evidence of drift, and was not affected by sex, age, race, or eye color. Overall, latanoprost caused a possible or definite increase in iris pigmentation in 12% of the 272 patients, all of whom had multicolored irides at baseline. One half of these patients with increased pigmentation withdrew before completing 1 year of therapy. Visual field, optic disc cupping, visual acuity, refractive error, conjunctival hyperemia, aqueous flare, anterior chamber cellular response, lens examination, blood pressure, heart rate, blood tests, and urinalysis were not appreciably altered.

**Conclusion:** Latanoprost safely and effectively reduces IOP for 1 year in patients of diverse nationalities, providing further evidence for its usefulness in chronic glaucoma therapy. *Ophthalmology* 1996;103:1916–1924

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Latanoprost, a prodrug of a 17-phenyl-substituted prostaglandin (PG)<sub>F<sub>2α</sub></sub> analog, when topically applied once daily at a concentration of 0.005%, is as effective and well tolerated as 0.5% timolol applied twice daily for 6 months in randomized, double-masked studies evaluating more than 800 patients with ocular hypertension or glaucoma.<sup>1-6</sup> However, to effectively treat chronic glaucoma, efficacy and safety must be demonstrated for more prolonged periods of time.

To provide this important longer-term information, this report describes the safety and efficacy of the first 198 patients who completed 1 year of treatment with 0.005% latanoprost topically applied once daily. These patients were recruited from three different parts of the world, enabling an international comparison of the relative efficacy and side effects of latanoprost.

## Methods

Patients were recruited from 10 centers in Scandinavia, 14 centers in the United Kingdom (UK), and 13 centers in the United States (US). To be eligible for the study, at least one eye of each patient had to meet the following criteria: (1) intraocular pressure (IOP) of at least 22 mmHg during treatment with no more than a single ocular hypotensive medication during the screening examination; (2) diagnosis of primary open-angle glaucoma, ocular hypertension, exfoliation syndrome, or pigment dispersion syndrome. If treated for their elevated IOP, patients discontinued their medication for a minimum of the following intervals before the baseline day: 3 weeks for beta-adrenergic antagonists, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists or carbonic anhydrase inhibitors. Patients previously treated with beta-adrenergic antagonists were not eligible to participate in the studies in Scandinavia or the UK, but were still eligible for the study in the US. Patients were ineligible for any of the following reasons: (1) younger than 40 years of age; (2) use of any ocular medications other than for glaucoma; (3) advanced glaucoma that would be at risk for progression during the washout period or during treatment with a single ocular hypotensive medication; (4) ocular conditions, including a history of acute angle-closure glaucoma, severe eye trauma, intraocular surgery or argon laser trabeculoplasty within 6 months, severe dry eye syndrome, or ocular inflammation/infection within 3 months; and/or (5) any unstable medical condition.

The first 6 months of the study were carried out in a randomized, double-masked fashion, with either 0.005% latanoprost applied once daily or 0.5% timolol applied twice daily to one or both eyes (depending on eligibility) for each patient. The latanoprost-assigned patients received active latanoprost at 8:00 PM and the vehicle at 8:00 AM each day for 6 months in the UK and US. In Scandinavia, the patients taking latanoprost were divided randomly into two groups. One group received the active latanoprost at 8:00 AM for the first 3 months, and at 8:00 PM for the second 3 months. The other group received latanoprost at 8:00 PM for the first 3 months and at 8:00 AM for the

second 3 months. Each center used standard procedures to assess the parameters that were evaluated.<sup>1-3</sup> Details of the 6-month, masked trial are described further in previous publications.<sup>1-5</sup>

After completion of 6 months of treatment, all centers were encouraged to give their subjects the option of continuing treatment with latanoprost in an open-label fashion for an additional 6 months. Each patient was given the option of applying 0.005% latanoprost once daily either in the morning (at approximately 8:00 AM) or the evening (at approximately 8:00 PM), with their choice of treatment time remaining unaltered during the course of the second 6-month, open-label trial. The patients receiving latanoprost in the morning were instructed not to take their drops in the morning of an examination day. Instead, the latanoprost was administered after their examination.

Patients returned for visits at 6½, 8, 10, and 12 months of treatment. Subjective side effects, visual acuity, refraction (if a change in visual acuity occurred), conjunctival hyperemia, slit-lamp biomicroscopy, IOP, and magnified color photography of the iris were assessed or performed on each visit in the morning. In addition, at the 12-month visit, the examination included automated visual field (Humphrey 24-2 or 30-2 [Allergan Humphrey, San Leandro, CA], Octopus G1 [Interzeag, Schlieren, Switzerland], or Competer [Bara Elektronik AB, Lund, Sweden]); dilated ophthalmoscopy, including assessment of the cup:disc ratio; blood pressure; heart rate; and diurnal (8:00 AM, 12:00 noon, and 4:00 PM) assessments of subjective side effects, conjunctival hyperemia, slit-lamp biomicroscopy, and IOP.

The iris photographs were reviewed by an independent panel of two or three ophthalmologists or scientists who were not investigators or examiners of any of the patients. The panel usually decided as a group whether a definite or suspect darkening of iris color occurred. The slightest suggestion of a change in pigmentation, including slight darkening or enlargement of a pre-existing brown area, was considered a change.

If the investigators believed that the latanoprost inadequately controlled the IOP, they were given the option of adding 0.25% or 0.5% timolol once or twice daily to their patients' regimen. If the addition of timolol did not adequately control the IOP, the patients were discontinued from the study and treated at the discretion of their ophthalmologist.

Adverse events were monitored carefully throughout the study. An adverse event was defined as any undesirable event occurring to a subject, whether or not it was considered related to the investigational drug. A serious adverse event was defined as potentially fatal, life threatening, sight threatening, permanently disabling, requiring hospitalization, cancer, or a drug overdose.

Blood samples collected at baseline and after 6 and 12 months of treatment were analyzed for the following: hematocrit level, hemoglobin level, mean corpuscular volume, mean corpuscular hemoglobin level, mean corpuscular hemoglobin concentration, erythrocyte count, leukocyte count, differential count, platelets, prothrombin, partial thromboplastin time, serum cholesterol level

Table 1. International Distribution and Reasons for Withdrawal from the Group of 272 Patients Who Began Therapy with Latanoprost by April 30, 1993\*

	Completed	Reason for Withdrawal							Total	% Withdrawal
		Inadequate IOP Control	Increased Iris Pigment	Other Ocular Reasons†	Systemic Medical Reasons	Option of Withdrawing at 6 Mos	Knowledge about Increased Iris Pigment§	Other Nonmedical Reasons		
Scandinavia	88	1	5	5	3	6‡	14‡	0	122 (45%)	28
United Kingdom	60	2	6	3	3	10	0	1	85 (31%)	29
United States	50	0	3	1	3	3	0	5	65 (24%)	24
Total	198 (73%)	3 (1%)	14 (5%)	9 (3%)	9 (3%)	19 (7%)	14 (5%)	6 (2%)	272 (100%)	27

IOP = intraocular pressure.

\* Values are number of patients.

† Includes blurred vision, photophobia, tearing, eye pain, punctate epithelial erosions, conjunctival hyperemia, chemosis, stinging, embolus in retinal artery, central retinal vein occlusion, branch retinal vein occlusion, and diabetic retinopathy.

‡ One of these patients was later found to show increased iris pigmentation.

§ Patients decided to withdraw after being informed that other patients in the study developed increased iris pigmentation.

(total, high-density lipoprotein, low-density lipoprotein), serum triglycerides, serum proteins, glucose value, creatinine level, urea level, bilirubin level, alkaline phosphatase, SGOT, SGPT, sodium, potassium, calcium, and chloride. Urinalysis included assessment of protein and glucose.

## Results

One hundred ninety-eight patients successfully completed 1 year of therapy with latanoprost by April 30, 1994. These 198 patients represent a subset of a total of 272 patients who began treatment with latanoprost in the randomized, masked study by April 30, 1993, and therefore had the potential of completing 1 year of treatment by April 30, 1994. Overall, the withdrawal rate was slightly less in the US compared with the other geographic areas

(Table 1). Of the 272 patients, 3 (1%) were withdrawn because of inadequate IOP control, all within the first 3 months of therapy (Tables 1 and 2). Excluding iris pigmentation, nine patients (3%) dropped out because of the development of adverse ocular side effects. Of these nine patients, six (67%) withdrew within the first 3 months, and 8 (89%) within the first 6 months of therapy (Tables 1 and 2). Symptoms or signs that may have represented an allergic or toxic reaction developed in only three of these nine patients (1% overall incidence). Of the 74 patients who withdrew from the study, 39 (53%) dropped out for nonmedical reasons, which included center deciding not to participate in the second 6-month, open-label trial; patients electing the option not to continue treatment during the second 6 months; information that an increase in iris pigmentation occurred in other patients; and lost to follow-up because of moving or traveling.

Table 2. Timing of and Reasons for Withdrawal of the 74 Patients Who Began Therapy with Latanoprost by April 30, 1993 but Did Not Complete 1 Year of Treatment\*

Time of Withdrawal (mos)	Reason for Withdrawal							Total
	Inadequate IOP Control	Increased Iris Pigment	Other Ocular Reasons†	Systemic Medical Reasons	Option of Withdrawing at 6 Mos	Knowledge about Increased Iris Pigment	Other Nonmedical Reasons	
≤3	3	0	6	6	0	0	3	18 (24%)
>3 and ≤6	0	2	2	3	19‡	3	3	32 (43%)
>6 and ≤9	0	10	1	0	0	10‡	0	21 (28%)
>9	0	2	0	0	0	1	0	3 (4%)
Total	3 (4%)	14 (19%)	9 (12%)	9 (12%)	19 (26%)	14 (19%)	6 (8%)	74 (100%)

IOP = intraocular pressure.

\* Values are number of patients. These 74 patients are a subset of the total 272 patients who began treatment by April 30, 1993.

† Includes blurred vision, photophobia, tearing, eye pain, punctate epithelial erosions, conjunctival hyperemia, chemosis, stinging, embolus in retinal artery, central retinal vein occlusion, branch retinal vein occlusion, and diabetic retinopathy.

‡ One of these patients was later found to show increased iris pigmentation.

Table 3. Demographics of Patients Completing 1 Year of Therapy

	Scandinavia (n = 88)	United Kingdom (n = 60)	United States (n = 50)	Total (n = 198)
Gender				
Men	37	40	24	101 (51%)
Women	51	20	26	97 (49%)
Age (yrs)				
Mean $\pm$ SD	68 $\pm$ 9	66 $\pm$ 9	61 $\pm$ 12	66 $\pm$ 10
Range	44–85	41–81	40–89	40–89
Race				
White	88	60	33	181 (91%)
Black	0	0	13	13 (7%)
Hispanic	0	0	4	4 (2%)

Forty-four percent of the 198 patients completing 1 year of treatment were from Scandinavia, with the remainder approximately evenly divided between the UK and US (Table 1). There were twice as many men compared with women in the UK, but approximately one half of the 198 patients were men from all three regions combined (Table 3). Mean age was 66 years, with patients slightly younger in the US. All patients from Scandinavia and the UK were white, whereas one third from the US were nonwhite (predominantly African-American) (Table 3).

More patients from the UK and US had ocular hypertension as opposed to primary open-angle glaucoma, whereas those from Scandinavia were approximately equally divided between these two groups (Table 4). Exfoliative glaucoma was present in 15% of patients from Scandinavia, but in less than 1% of patients from the UK and US. Unilateral treatment was given to approximately one fifth of patients overall, ranging from one third of patients in Scandinavia to only 4% of those in the US. Because of the difference in selection criteria among the geographic regions, none of the patients from Scandinavia

or the UK, but two thirds of the patients from the US, were treated previously with beta-adrenergic blockers (Table 4). As specified by the protocol, all patients from the UK and the US took latanoprost in the evening during the first 6 months, whereas patients from Scandinavia were evenly divided between morning and evening dosing. However, two thirds of patients decided on morning dosing during the second 6 months.

Intraocular pressure was significantly ( $P < 0.0001$ ) reduced by  $8 \pm 3$  mmHg (mean  $\pm$  standard deviation; 32%) during the course of treatment (Figs 1 and 2). The IOP reduction did not significantly change comparing 6- and 12-month values. The reduction of diurnal IOP measurements from baseline was more pronounced in Scandinavia (from  $25.5 \pm 3.0$  mmHg to  $16.8 \pm 2.5$  mmHg) and the UK (from  $25.5 \pm 3.0$  mmHg to  $17.7 \pm 2.4$  mmHg), compared with the US (from  $24.9 \pm 2.9$  mmHg to  $18.0 \pm 3.1$  mmHg) at 1 year. Sex, age, race, previous glaucoma therapy, or eye color did not affect the IOP response. Of the 198 patients, 12 (6%) received timolol in addition to the latanoprost. Even if the uncontrolled IOP of these 12

Table 4. Baseline Characteristics of the Pairs of Eyes of Each Patient Completing 1 Year of Therapy

	Scandinavia (n = 88)	United Kingdom (n = 60)	United States (n = 50)	Total (n = 198)
Diagnosis				
Ocular hypertension	36	35	26	97 (49%)
Primary open-angle glaucoma	35	23	18	76 (38%)
Exfoliation glaucoma	13	0	1	14 (7%)
Pigmentary glaucoma	1	0	2	3 (2%)
Mixed types	3	2	3	8 (4%)
No. of eligible eyes receiving treatment per patient				
1 eye	29	13	2	42 (21%)
Both eyes	59	47	48	156 (79%)
Prior glaucoma therapy				
$\beta$ -Adrenergic blocker	0	0	33	33 (17%)
Adrenergic agonist	2	4	3	9 (5%)
Cholinergic agonist	5	2	4	11 (6%)
Carbonic anhydrase inhibitor	2	0	3	5 (3%)

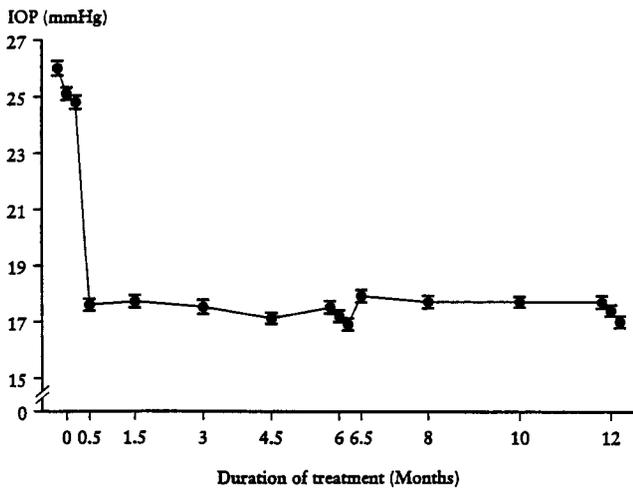


Figure 1. Effect on intraocular pressure (IOP) of 0.005% latanoprost applied once daily to one or both eyes in each of 198 patients with elevated IOP completing 1 year of therapy. Each point represents the mean IOP of 184 to 198 patients, with limits of  $\pm$  standard error of the mean. All values during treatment were significantly ( $P < 0.0001$ ) reduced compared with baseline measurements.

patients before the addition of timolol was carried forward through the 12 months of therapy, the latanoprost-induced IOP reduction would not be significantly altered. In the 42 patients receiving unilateral therapy, the IOPs in the contralateral untreated eyes were not significantly altered during the course of the study.

Ten patients had serious adverse events, none of which were believed to be secondary to the latanoprost treatment (Table 5). The incidence of adverse events was not different comparing the first 6 months with the second 6 months of treatment. In general, patients recovered from most adverse events without sequela, except for the increase in iris pigmentation.

In addition to the 14 patients who withdraw from the study because of increased iris pigmentation before completing 1 year of therapy, and the 2 additional patients who withdrew for other reasons and later had this increased pigmentation (Tables 1 and 2), 6 (3%) of the 198 patients completing 1 year of therapy definitely showed this change, and an additional 10 patients (5%) were suspects (Table 6). Therefore, 22 (8%) of the 272 patients who began treatment by April 30, 1993, had a definite increase in iris pigmentation. As a worse-case scenario analysis by including all definite and suspect cases, and by adding to the 198 patients only those 16 patients with increased pigmentation who withdrew before completing 1 year of treatment, without including any other patient who withdrew, 32 (15%) of 214 patients demonstrated a possible or definite increase in iris pigmentation. Of these 32 patients, baseline iris color was blue/gray-brown in 7 (22%), green-brown in 22 (69%), and yellow-brown in 3 (9%). An increase in iris pigmentation was not observed in any patient with the following baseline iris colors: blue/gray, blue/gray with slight brown, or brown. The pigmentary changes occurred more frequently in patients in the UK than those

in either Scandinavia or the US (Table 6). The pigmentary change usually was noted between 6 and 12 months of treatment, at which time the patient was withdrawn from treatment (Table 2). A retrospective review of the photographs of these patients demonstrated that the first subtle evidence of increased iris pigmentation often occurred a few months earlier. Variability in photographic technique occasionally necessitated two sets of photographs to confirm apparent changes. Iris nevi and freckles, carefully documented photographically at baseline, did not change with latanoprost treatment.

Ocular symptoms and signs were graded as mild with few exceptions. The symptoms and signs were reported more frequently during the first 6 months than during the second 6 months of therapy. Overall, mean conjunctival hyperemia was graded as slight at baseline, and did not appreciably change throughout the course of therapy (Table 7). No change in mean visual acuity or refractive error occurred during the course of therapy. During the 12 months of treatment, slight aqueous flare was noted at least once in three patients (2%). A few cells in the anterior chamber were observed at least once at baseline or during the 12 months of therapy in ten patients (5%), two of whom had cells observed on the baseline day. No appreciable changes were observed for any of the following: cup:disc ratio; visual fields; eyelids; conjunctiva; cornea; iris (except for pigmentation); lens; vitreous; retina; blood pressure; heart rate; and blood and urine analyses. Because only three visual fields were obtained on each patient (at baseline, 6 months, and 1 year), definite progressive changes were difficult to determine in view of inherent variability. However, no obvious progressive glaucomatous defects were apparent.

## Discussion

This study demonstrates that latanoprost applied once daily safely and effectively reduces IOP for 1 year in

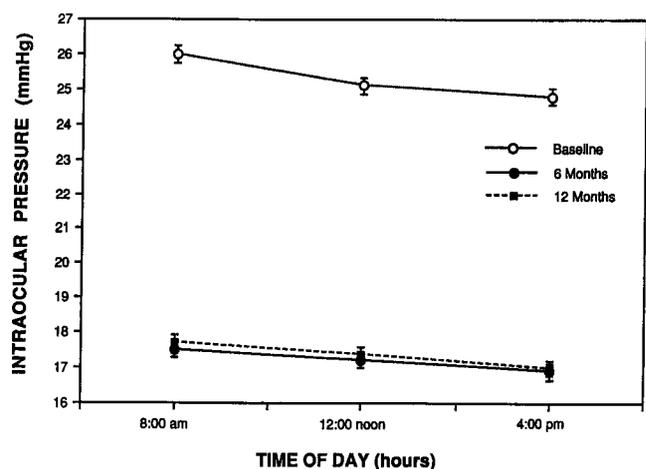


Figure 2. Diurnal intraocular pressure measurements at baseline and after 6 and 12 months of treatment with 0.005% latanoprost applied once daily to 198 patients with elevated intraocular pressure. Each point represents the mean of 198 patients with limits of  $\pm$  standard error of the mean. There was no significant difference comparing 6- and 12-month values.

Table 5. Number of Patients with Adverse Events Not Necessarily Related to Treatment) in Those Completing 1 Year of Therapy

	Scandinavia (n = 88)	United Kingdom (n = 60)	United States (n = 50)	Total (n = 198)
Serious*				
Ocular†	0	0	0	0
Nonocular	5	2	3	10§
Not serious‡				
Ocular†	10	20	0	30
Nonocular	15	15	12	42

\* Defined as potentially fatal, life-threatening, sight threatening, permanently disabling, requiring hospitalization, cancer, or a drug overdose.  
† Patients with ocular adverse events are indicated only if the event occurred in an eye treated with latanoprost.  
‡ Twelve patients had both ocular and nonocular adverse events; 23 patients had more than one adverse event.  
§ Includes abdominal pain, broken right hip, surgery for inguinal hernia, esophageal cancer, angina pectoris, chest pain, breast cancer, hospitalization for liver biopsy, gynecomastia, and hospitalization for colon resection for abscess.

patients with ocular hypertension and open-angle glaucoma. The IOP reduction was maintained without evidence of drift during the 1 year of treatment. The 30% to 35% reduction of IOP is comparable to that achieved with nonselective beta-adrenergic blockers and verifies previous randomized, masked studies demonstrating similar efficacy compared with timolol for 6 months.<sup>1-6</sup> Only 1% of the 272 patients receiving latanoprost dropped out due to inadequate IOP control, and only 6% of the 198 patients completing 1 year of treatment were given supplemental timolol to maintain adequate control. In contrast, IOP was reduced by 14% after 1 year of treatment with dorzolamide in an open-label trial.<sup>7</sup> In a 1-year study evaluating dorzolamide and betaxolol, 10% to 15% of patients dropped out because of insufficient IOP reduction, and another 30% to 35% required supplemental medications to achieve adequate control.<sup>8</sup> Of prostaglandin analogs evaluated in clinical trials, latanoprost offers the greatest separation between ocular hypotensive efficacy and adverse side effects.<sup>6</sup>

The exceedingly low drop-out rate secondary to inadequate IOP control (1%) or ocular reasons other than in-

creased iris pigmentation (3%) is at least as low as that found with nonselective beta-blockers<sup>9</sup> and considerably better than the drop-out rates found in long-term trials with the following medications: epinephrine, 35% to 50%<sup>10,11</sup>; pilocarpine, approximately 90% of patients younger than 30 years of age or with significant cataracts; apraclonidine, 15% to 50%<sup>12-16</sup>; and oral carbonic anhydrase inhibitors, 50%.<sup>17</sup> Unlike epinephrine or apraclonidine, which frequently produce allergic or toxic reactions requiring discontinuation of treatment, latanoprost produced an allergic reaction in no more than 1% of the 272 patients evaluated in this study. Unlike the known potential systemic side effects of beta-adrenergic blockers on pulmonary and cardiac function, latanoprost has not been demonstrated to, and is not expected to, produce any systemic side effects, based on pharmacokinetic considerations.<sup>18,19</sup>

This study demonstrates that an increase in iris pigmentation occurs in 8% to 15% of eyes, beginning 3 to 12 months after initiation of treatment. This pigmentary change occurred more frequently in the UK than in either Scandinavia or the US, perhaps due to the greater num-

Table 6. Incidence of Possible Increase in Iris Pigmentation Relative to Baseline Iris Color in Those Patients Completing 1 Year of Therapy\*

Iris Color	Scandinavia (n = 88)	United Kingdom (n = 60)	United States (n = 50)	Total (n = 198)
Blue/gray	0/39	0/10	0/3	0/52 (0%)
Blue/gray with slight brown	0/29	0/14	0/8	0/51 (0%)
Blue/gray-brown	1/9	2/19	1/7	4/35 (11%)
Green with slight brown	0/1	0/0	0/0	0/1 (0%)
Green-brown	3/7	7/13	0/7	10/27 (37%)
Brown (in whites)	0/3	0/2	0/8	0/13 (0%)
Yellow-brown (in whites)	0/0	2/2	0/5	2/7 (29%)
Brown (in blacks)	0/0	0/0	0/12	0/12 (0%)

\* The numerator is the number of patients with possible darkening of eye color; the denominator is the number of patients with specified eye color.

Table 7. Relative Conjunctival Hyperemia in Those Patients Completing 1 Year of Therapy\*

Time	Scandinavia (n = 88)	United Kingdom (n = 60)	United States (n = 50)	Total (n = 198)
Baseline	0.5 ± 0.3	0.3 ± 0.4	0.3 ± 0.4	0.4 ± 0.4
6 mos	0.6 ± 0.4	0.5 ± 0.5	0.4 ± 0.4	0.5 ± 0.4
12 mos	0.6 ± 0.4	0.4 ± 0.4	0.3 ± 0.4	0.4 ± 0.4

\* Values represent the mean ± standard deviation of the maximum conjunctival hyperemia response determined for each patient on the specified day of the study. If both eyes were treated, the eye demonstrating the greatest hyperemia was used.

ber of mixed-colored ("at risk") irides at baseline. Based on experiments in rabbits and monkeys, this increased pigmentation is secondary to enhanced melanogenesis (increase of melanin within the melanocytes), but is not due to proliferation of melanocytes (Albert et al, unpublished data; Pharmacia and Upjohn, unpublished data). Pre-existing iris freckles or nevi do not change during latanoprost treatment. At this time, only mixed-colored irides at baseline have been reported to demonstrate the change, making the iris uniformly darker. Irises with a uniform blue/gray or brown color did not appear to have the pigmentary changes after 1 year of treatment. However, because of variability in photographic technique, it is possible that some brown irides may become slightly darker, which would be difficult to document photographically. This increased pigmentation may be a result of prostaglandins substituting for deficient sympathetic tone (Camras et al, unpublished data; presented at the ARVO Annual Meeting, Ft. Lauderdale, May 1995).<sup>4,6</sup> Although it appears to be harmless, and may represent a cosmetic problem only in those patients with irides treated unilaterally, it must be emphasized that patients with increased iris pigmentation discontinued latanoprost treatment after no more than 1 year of treatment. The effect of continued treatment in these patients is not known, but must be evaluated in further studies. Although iris melanocytes appear to be continent (i.e., do not release pigment to neighboring cells), and pigmentary changes have not been observed elsewhere in the eye (specifically the trabecular meshwork or choroid), definitive conclusions about possible long-term adverse effects of the pigment changes in the iris cannot be made without these additional studies. Because of these uncertainties, it would be prudent to exercise caution using latanoprost in "at-risk" eyes until more experience with long-term use is acquired.

The large number of patients evaluated in three geographic regions of the world indicates that the efficacy and safety of latanoprost are independent of nationality, ethnic group, sex, age, iris color, or previous glaucoma therapy. Although the efficacy of some drugs is influenced, in part, by pigment binding,<sup>20,21</sup> the current study demonstrates that latanoprost maintains its potency and efficacy in both blue and brown eyes.

This study has similar problems inherent in any open-

label trial. However, the first 6 months of the trial was performed in a double-masked fashion, demonstrating efficacy and tolerance comparable to timolol,<sup>1-6</sup> and the 1-year data compare favorably to similar data from other open-label trials with nonselective beta-adrenergic blockers.<sup>9</sup> Although the overall drop-out rate is moderately high, only 4% dropped out for ocular reasons, excluding increased iris pigmentation, and 72% of patients withdrew for either nonmedical reasons or for the increase in iris pigmentation.

In conclusion, latanoprost, when topically applied once daily, is a safe and effective agent for treating ocular hypertension and primary open-angle glaucoma. It is more potent (used at 1/100 the concentration of timolol) and at least as effective as any medication currently used in glaucoma therapy. Advantages over beta-adrenergic blockers include its apparent lack of systemic side effects and its mechanism of action on outflow.<sup>22-24</sup> The increase in iris pigmentation appears harmless, but must be studied further. If results in these 198 patients completing 1 year of treatment are confirmed in larger, longer-term studies, latanoprost will have great potential of becoming a new first-line treatment for glaucoma.

## Appendix

### Members of the Latanoprost Study Group:

#### Scandinavia

Center of Eye Surgery (Bergen, Norway): Principal Investigator: H. Aasved, MD; Co-investigator: P. Jangard, MD; *Gentofte Hospital (Hellerup, Denmark)*: Principal Investigator: H. Lund-Andersen, MD; Co-investigator: P. Flesner, MD; *Huddinge University Hospital (Huddinge, Sweden)*: Principal Investigator: M. Söderström, MD; *Lund University Hospital (Lund, Sweden)*: Principal Investigator: B. Ehinger, MD; Co-investigators: C. Holmin, MD, E. Bengtsson-Stigmar, MD; *Malmö General Hospital (Malmö, Sweden)*: Principal Investigator: A. Heijl, MD; Co-investigator: K. G. Gundersen, MD; *Oulu University Hospital (Oulu, Finland)*: Principal Investigator: J. Airaksinen, MD; Co-investigator: A. Tuulonen, MD;

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