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A comparison of morning and evening instillation of a combination travoprost 0.004%/timolol 0.5% ophthalmic solution

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PURPOSE. *To compare the intraocular pressure lowering efficacy and side effect profile of travoprost 0.004%/timolol 0.5% ophthalmic solution dosed in the morning and evening.*
METHODS. *This was a multicenter, prospective, randomized, double-masked, parallel group clinical study of 92 patients with open-angle glaucoma (with or without pseudoexfoliative or pigmentary glaucoma) or ocular hypertension. After a washout of existing glaucoma medications, patients were randomly assigned to receive one drop of travoprost 0.004%/timolol 0.5% in the morning or evening for 6 weeks. The main outcome measures were mean intraocular pressure (IOP) assessed at 9 am, 11 am, and 4 pm, and safety variables.*
RESULTS. *Travoprost 0.004%/timolol 0.5% ophthalmic solution, dosed in the morning or evening, controlled IOP consistently throughout the day. Mean IOP ranged from 16.5 to 16.7 mmHg in the morning treatment group and from 16.1 to 17.2 mmHg in the evening treatment group. Travoprost 0.004%/timolol 0.5% ophthalmic solution produced statistically significant and clinically relevant reductions in IOP from baseline; mean reductions ranged from approximately 8 to 10 mmHg (32% to 38%). Travoprost 0.004%/timolol 0.5% ophthalmic solution was safe and well tolerated with the most frequently reported adverse event being ocular hyperemia, which occurred in 12.5% of patients in the morning treatment group and 13.6% of patients in the evening treatment group.*
CONCLUSIONS. *Travoprost 0.004%/timolol 0.5% given once daily, either in the morning or evening, is a safe and effective treatment for open-angle glaucoma and ocular hypertension. It may be beneficial for patients judged to be inadequately controlled on a prostaglandin analogue or ophthalmic beta-blocker alone. (Eur J Ophthalmol 2006; 16: 407-15)*

KEY WORDS. *Glaucoma, Prostaglandin, Beta-blocker, Compliance, IOP, Travoprost, Timolol*

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INTRODUCTION

Travoprost is a prostaglandin analogue that is a highly selective agonist for the prostaglandin FP receptor (1, 2) and is used clinically for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication. As with other prostaglandin analogues, travoprost is believed to exert its effect on IOP by increasing outflow of aqueous humor via the uveoscleral drainage route and possibly also by a reduction in resistance in the trabecular meshwork (3-6). It has been demonstrated to provide effective reductions in IOP with

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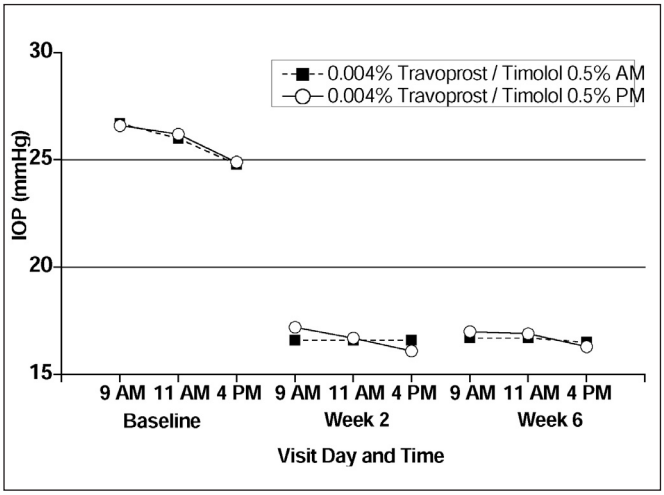

Fig.1 - *Mean IOP for Travoprost 0.004%/Timolol 0.5% AM and Travoprost 0.004%/Timolol 0.5% PM (Per Protocol Data).*

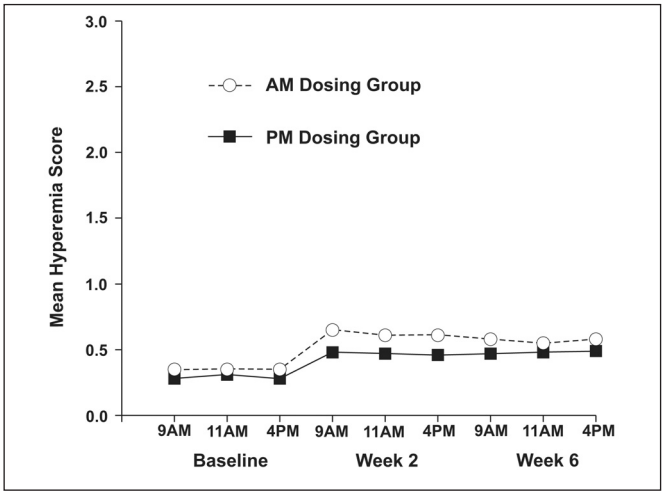

Fig. 2 - *Mean ocular hyperemia scores (0= None; 1= Mild; 2= Moderate; 3= Severe).*

once daily dosing, in the evening (7, 8). However, assessment of diurnal pressure curves after repeated dosing with travoprost has demonstrated a long duration of action for the drug and indicates that time of dosing is probably not critical (9).

Travoprost has been shown to produce an additional reduction in IOP when used in combination with the topical ophthalmic beta-blocker, timolol (10). This adjunctive effect on IOP is to be expected from a theoretical point of view since ophthalmic beta-blockers lower IOP by reducing the rate of aqueous humor formation (11). Thus, the two drugs have different and complementary modes of

TABLE I - DEMOGRAPHIC STATISTICS BY TREATMENT GROUP

	Total		AM Group		PM Group		
	n	%	n	%	n	%	p-value*
Total	91	100.0	48	52.7	43**	47.3	
Age							
<65	43	47.3	20	41.7	23	53.5	0.2594
≥65	48	52.7	28	58.3	20	46.5	
Gender							
Male	46	50.5	22	45.8	24	55.8	0.3418
Female	45	49.5	26	54.2	19	44.2	
Ethnicity							
Caucasian	90	98.9	48	100.0	42	97.7	0.4725
Other	1	1.1	0	0.0	1	2.3	
Iris Colour							
Brown	58	63.7	31	64.6	27	62.8	0.9802
Hazel/Green	13	14.3	6	12.6	7	16.3	
Blue/Grey	20	22.0	11	22.9	9	20.9	
Diagnosis							
OH	12	13.2	8	16.7	4	9.3	0.5118
OAG	70	76.9	34	70.8	36	83.7	
Pigmentary glaucoma	2	2.2	1	2.1	1	2.3	
Pseudoexfoliation glaucoma	7	7.7	5	10.4	2	4.7	

*Chi-square test or Fisher's exact test
**Fourty-four patients were randomized in the evening dosing group. One discontinued the study prior to collection of any on-therapy study visit data and therefore was excluded from the intent-to-treat analysis

action. When used as first-line therapy for open-angle glaucoma and ocular hypertension, timolol is often dosed twice daily. However, the use of a fixed dose combination of timolol and a prostaglandin analogue in a single ophthalmic solution dosed once daily has been demonstrated to provide a significant additive effect (12) and has the potential to improve patient compliance.

This study was designed to evaluate the efficacy and side effect profile of a fixed combination ophthalmic solution of travoprost 0.004% and timolol 0.5%, given once daily, in patients with open-angle glaucoma or ocular hypertension and to determine whether there is any significant difference between morning (am) or evening (pm) dosing. The primary objective was to demonstrate that morning and evening dosing produce equivalent IOP-lowering efficacy.

METHODS

Design and setting

This study was a multicenter, prospective, randomized, double-masked, parallel-group clinical comparison.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Institutional Review Boards. Study participants gave informed consent before initiation of any study-related procedures.

Patients and intervention

Patients eligible for inclusion were of either sex or any ethnic group, diagnosed with either open-angle glaucoma (with or without pseudoexfoliative or pigmentary glaucoma) or ocular hypertension, and were currently treated with one or more IOP-lowering medications. After a suitable washout period, the length of which was based on the medications currently being used, the mean IOP in at least one treated eye had to be greater than or equal to 24 mmHg at 9 am and greater than or equal to 21 mmHg at 11 am and 4 pm on each of two eligibility visits. If only one eye qualified, then this had to be the same eye at each eligibility visit. In addition, the mean IOP in either eye could be no greater than 36 mmHg at either visit.

Women of childbearing potential were excluded from the study if they were currently pregnant, had a positive urine pregnancy test at the screening visit, intended to

TABLE II - MEAN IOP, IOP CHANGE FROM BASELINE, ECC

	Baseline			Combined*			Week 2			Week 6		
	9AM	**11AM**	**4PM**	**9AM**	**11AM**	**4PM**	**9AM**	**11AM**	**4PM**	**9AM**	**11AM**	**4PM**
AM Group												
Mean	26.7	26.0	24.8	16.7	16.6	16.6	16.6	16.6	16.6	16.7	16.7	16.5
N	43	43	43	42	42	42	41	42	42	40	40	40
PM Group												
Mean	26.6	26.2	24.9	17.1	16.8	16.2	17.2	16.7	16.1	17.0	16.9	16.3
N	40	40	40	39	40	40	39	40	40	39	37	36
Difference	0.1	-0.2	-0.1	-0.4	-0.2	0.4	-0.6	-0.1	0.5	-0.3	-0.2	0.2
p-value	0.77	0.68	0.78	0.53	0.80	0.59	0.45	0.85	0.49	0.66	0.78	0.75
Upper 95% CI	1.1	0.8	0.8	0.9	1.2	1.8	0.9	1.3	2.0	1.1	1.3	1.7
Lower 95% CI	-0.8	-1.2	-1.-1	-1.8	-1.6	-1.0	-2.0	-1.6	-1.0	-1.8	-1.7	-1.2

CI= Confidence interval. Estimates based on least squares means and confidence intervals from repeated measures of analysis of variance
Baseline estimates obtained from a separate model
*Combined = Results pooled across Weeks 2 and 6

become pregnant, were breast feeding, or were not using highly effective birth control measures. Patients were also excluded if they had a history of chronic or recurrent severe inflammatory eye disease; a history of ocular trauma within the preceding 6 months or ocular infection or inflammation within the preceding 3 months; a history of clinically significant or progressive retinal disease, other severe ocular pathology that would have precluded the administration of a topical prostaglandin analogue, or severe or serious hypersensitivity to any components of the study medication; had undergone intraocular surgery within the preceding 6 months or ocular laser surgery within the preceding 3 months; or had a best-corrected visual acuity worse than 0.6 logMAR score, anterior chamber angle grade less than Grade 2 (measured by gonioscopy), a cup/disc ratio greater than 0.8, or severe central visual field loss in either eye. In addition, patients could not take part if they were taking glucocorticoids or any additional topical or systemic ocular hypotensive medication; had a history of severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease or bronchial asthma or severe chronic obstructive pulmonary disease; or had less than 30 days stable dosing of any non-glaucoma medications or substances on a chronic basis that might affect IOP.

Patients were randomized to one of two treatment groups in a 1:1 ratio by means of a computer-generated randomization schedule. One group received one drop of travoprost 0.004%/timolol 0.5% instilled at 9 am ± 1 hour in the morning (am treatment group), while the other group received one drop of travoprost 0.004%/timolol 0.5% instilled at 9 pm ± 1 hour in the evening (pm treatment group). Eligible patients were randomized sequentially at each study site. In order to maintain double-masked conditions, timolol vehicle was dosed in the morning in patients in the pm treatment group and in the evening in patients in the am treatment group.

Main outcome measures

The primary efficacy variable used in this study was an assessment of mean IOP at the 9 am, 11 am, and 4 pm time points (±1 hour) at week 2 and week 6. If both eyes were dosed, the worse evaluable eye was selected for analysis. This was defined as the eye with the higher IOP at 9 am averaged across the two eligibility visits (followed by the eye with the higher IOP at 11 am and then at 4 pm if the pressures at the preceding times were equal). If all pressures were equal then the right eye was used for analysis. Secondary efficacy variables measured were

TABLE III - MEAN IOP, IOP CHANGE FROM BASELINE, AND PERCENT IOP CHANGE FROM BASELINE (per Protocol Data)

	Baseline			Combined*			Week 2			Week 6		
	9AM	**11AM**	**4PM**	**9AM**	**11AM**	**4PM**	**9AM**	**11AM**	**4PM**	**9AM**	**11AM**	**4PM**
AM Group												
Mean	26.7	26.0	24.8	16.7	16.6	16.6	16.6	16.6	16.6	16.7	16.7	16.5
n	43	43	43	42	42	42	41	42	42	40	40	40
Mean change				-10.1	-9.4	-8.3	-10.01	-9.45	-8.2	-10.1	-9.34	-8.34
Mean % change				-37.8	-36.0	-33.5	-37.8	-36.4	-33.2	-37.8	-36.0	-33.9
PM Group												
Mean	26.6	26.2	24.9	17.1	16.8	16.2	17.2	16.7	16.1	17.0	16.9	16.3
n	40	40	40	39	40	40	39	40	40	39	37	36
Mean change				-9.5	-9.4	-8.8	-9.4	-9.5	-8.8	-9.6	-9.3	-8.7
Mean % change				-35.7	-35.9	-35.1	-35.1	-36.2	-35.1	-36.1	-35.1	-34.4

*Estimates based on descriptive statistics

IOP change (actual and percentage) from baseline. A target IOP responder analysis was also conducted, to be consistent with other recent published clinical studies involving ocular hypotensive medications (7, 8, 13-15).

Safety was assessed by measurement of visual acuity (best-corrected logMAR); scoring of ocular signs (cornea, iris/anterior chamber, lens, flare, cells), ocular hyperemia (scale 0 = none; 1 = mild; 2 = moderate; 3 = severe), dilated fundus parameters (vitreous, retina/macula/choroid, optic nerve); measurement of cup/disc ratio; and measurement of cardiovascular parameters (pulse rate, systolic blood pressure, and diastolic blood pressure). An incidence of hyperemia was recorded if the patient complained or discontinued the study due to ocular hyperemia. Other adverse events were also recorded.

The statistical objective of this study was to compare the IOP-lowering efficacy of morning versus evening dosing of travoprost 0.004%/timolol 0.5% ophthalmic solution. A confidence interval–based test of equivalence was used to make the comparison. Hypothesis tests were performed using repeated measures of analysis of variance. For the primary statistical objective, a 95% confidence interval about the treatment effect was constructed based on the analysis of variance. The two dosing regimens were to be declared equivalent if the confidence interval limits were within ±2.5 mm Hg. In active-controlled glaucoma studies, an equivalence criterion of 1.5 mmHg is commonly used. In this study we were interested in whether a substantial difference between the two dosing regimens existed and so the broader criterion was used. Descriptive statistics were calculated for IOP, change in IOP from baseline, and percentage change in IOP from baseline. Mean IOP change from baseline was also estimated using a repeated measures analysis of variance. The sample size of 42 evaluable patients per treatment group was determined to provide an 80% coverage probability that a 95% two-sided confidence interval would fall within ±2.5 mmHg and a greater than 80% power to detect a difference of 2.5 mmHg between treatment groups. These estimates were based on a standard deviation for IOP of 3.5 mmHg and a two-sample t-test conducted at a 5% chance of Type 1 error. All statistical analyses were completed using SAS for Windows version 8.2 software.

Three data sets were used for analysis. All patients enrolled in the study who received at least one dose of study medication were considered evaluable for analysis of adverse events. All patients who received study medication and completed at least one on-therapy study visit were considered evaluable for intent-to-treat analysis (ITT). All patients who received study medication, completed at least one on-therapy study visit, and satisfied protocol inclusion and exclusion criteria were considered evaluable for the per protocol analysis (PP). For the ITT data set IOP results from previous visits were carried forward for missed patients and discontinued patients. No data were carried forward in the PP data set.

RESULTS

Ninety-two patients were randomized and received study medication: 48 in the am treatment group and 44 in the pm treatment group. Seventy patients (77.2%) were diagnosed with open-angle glaucoma, 12 (13.0%) with ocular hypertension, 2 (2.2%) with pigmentary glaucoma, and 7 (7.6%) with pseudoexfoliation glaucoma. Mean age at enrollment was 63.9 years (range: 36 to 84 years). All 92 patients were included in the adverse event analysis.

TABLE IV - MOST FREQUENT TREATMENT RELATED OCULAR ADVERSE EVENTS

	AM Group n = 48		**PM Group n = 44**		**Total n = 92**	
Adverse event	n	%	n	%	n	%
Hyperemia	6	12.5	6	13.6	12	13.0
Foreign body sensation	2	4.2			2	2.2
Pruritus	1	2.1	3	6.8	4	4.3
Blurred vision	2	4.2			2	2.2

Ninety-one patients (48 in the am treatment group and 43 in the pm treatment group) were available for the ITT data set (one patient discontinued prior to collection of any on-therapy study data) and 83 patients (43 in the am treatment group and 40 in the pm treatment group) were available for the PP data set. The remaining eight patients (8.8%) were excluded from the PP analysis due to protocol violations, which included non-qualifying IOP, measurement/visit outside study window, inadequate time interval from dosing to IOP measurement, non-dosing, insufficient washout, and use of excluded concomitant medication.

Demographic details for all patients in the ITT data set are given in Table I. There were no statistically significant differences between treatment groups for mean age (p=0.3154), age category (<65, 65+) (p= 0.2594), sex (p=0.3418), race (p=0.4725), iris color (p=0.9802), or diagnosis (p=0.5118). Mean baseline IOP in the ITT data set ranged across the day from 24.5 mmHg to 26.7 mm Hg. No significant difference was observed between groups for baseline IOP in either the ITT or PP data sets.

Travoprost 0.004%/timolol 0.5% ophthalmic solution, dosed either once daily in the morning or once daily in the evening, controlled IOP consistently throughout the day. In the am treatment group, mean on-treatment IOP ranged from 16.5 to 16.7 mmHg in the PP data set, while in the pm treatment group the corresponding figures were 16.1 to 17.2 mm Hg. All of the two-sided 95% confidence limits were within ± 2.5 mm Hg, the limit of clinical relevance used to establish equivalence in this study, in both the PP and ITT data sets. Mean IOP was less variable throughout the day following morning dosing (Tab. II).

Travoprost 0.004%/timolol 0.5% ophthalmic solution produced statistically significant and clinically relevant reductions in IOP from baseline, with mean reductions ranging from approximately 8 to 10 mmHg (Tab. III). This equates to IOP reductions of 32% to 38% relative to baseline. In addition, up to 29/42 (69.0%) patients in the PP data set achieved IOP levels <18 mmHg at any assessment time ranging from 24/40 (60.0%) in the am treatment group to 27/40 (67.5%) in the pm treatment group. There was no statistically significant difference between the am treatment group and pm treatment group with regard to the percentage of patients who achieved an IOP <18 mmHg at all six measurements (p=0.7304). Repeated measures analysis of variance revealed no statistically significant interactions between age category (<65, 65+) (p>0.25), sex (p>0.35), iris color (p>0.05), or diagnosis (p>0.25) and treatment in either the PP or ITT data sets. Travoprost 0.004%/timolol 0.5% ophthalmic solution administered once daily was safe and well tolerated in this group of patients, based upon a review of adverse events and an assessment of ocular and cardiovascular parameters. Similar side effect profiles were observed comparing morning and evening dosing.

A total of 28 patients dosed with the study medication experienced adverse events. There were no clinically relevant differences in the demographic characteristics between patients with and without adverse events. The most frequently reported adverse event was ocular hyperemia, which occurred in 6/48 (12.5%) patients in the am treatment group and 6/44 (13.6%) patients in the pm treatment group (Tab. IV). There was no clinically relevant difference comparing the mean hyperemia scores at week 2 and week 6 between the two treatment groups. However, each occurrence was judged to be mild or moderate in intensity at all evaluation points (Fig. 2). Three patients discontinued treatment due to adverse events (one case of ocular hyperemia and one case of asthma in the am treatment group; one case of ocular edema with ocular hyperemia in the pm treatment group).

No patient experienced a clinically relevant change in best-corrected visual acuity (a decrease of three or more lines from baseline) and there were only three incidents of clinically relevant increases in ocular signs (one superficial punctate epitheliopathy and two cases of flare). All were considered mild and did not interrupt continuation in the study. No patient experienced a clinically relevant change in dilated fundus parameters or in cup/disc ratio. No clinically relevant changes in pulse rate were identified, while one case of a clinically relevant increase in systolic blood pressure, one case of a clinically relevant increase in diastolic blood pressure, and one case of a clinically relevant decrease in diastolic blood pressure were recorded. These changes in cardiovascular parameters were not considered to warrant discontinuation of treatment.

DISCUSSION

Combining travoprost and timolol into a single ophthalmic solution is appealing since it could provide a more marked reduction in IOP than either drug alone, while maintaining the convenience and simplicity of instilling a single preparation once daily. A previous study by Barnebey and colleagues demonstrated that travoprost

0.004%/timolol 0.5% fixed combination ophthalmic solution dosed once daily in the morning was more effective in reducing IOP than either travoprost 0.004% ophthalmic solution dosed once daily in the evening or timolol 0.5% dosed twice daily (16). Timolol is indicated for once or twice daily use but in clinical practice it is often dosed twice daily. It, therefore, seems possible that if travoprost and timolol were to be combined into a fixed dose combination product, to be given once a day to patients, the additive effect, seen when the two drugs are given together but separately, would not last for a full 24-hour period and that any fall in IOP observed might be dependent on the time of dosing. Indeed, studies using a fixed combination product of another prostaglandin analogue, latanoprost, and timolol have indicated that, although good diurnal control of IOP is maintained, the pressure reductions produced are not as great as those obtained using the two drugs concomitantly, with timolol given twice daily (17, 18). Another study has indicated that, although a fixed dose combination of latanoprost and timolol was effective when dosed either morning or evening, there was a trend for greater daytime IOP reductions with evening dosing and lower night-time pressures after morning dosing (19).

In the current study, a fixed dose combination of travoprost 0.004%/timolol 0.5% dosed once daily, in the morning or the evening, produced clinically relevant and statistically significant reductions in IOP from baseline at 9 am, 11 am, and 4 pm. No significant difference in IOP-lowering efficacy was observed between morning or evening dosing with the product. Limitations of the study were the small sample size and the fact that all measurements were conducted during normal office hours. A full circadian curve such as the study performed by Konstas et al (19) would provide more comprehensive results from which to make comparisons of morning and evening dosing. Circadian studies present a number of technical and logistic challenges, however. The diurnal IOP variation in the current study, even for the pm group, was small, and well within the limits of variation seen in studies of the individual drugs (7, 8) and in normal eyes (20) and is unlikely to have a clinical impact.

Reductions in mean IOP from baseline up to 38% were observed in the current study. Hughes et al reported similar reductions in IOP from baseline with travoprost 0.004%/timolol 0.5% fixed combination (up to 37%) compared with concomitant dosing of the two agents (up to 38%) (21). Another study by Schuman and colleagues showed reductions in IOP from baseline of up to 33% for the travoprost 0.004%/timolol 0.5% fixed combination solution and up to 35% for the two agents dosed concomitantly (22). The percentage of patients in the PP dataset of the current study achieving an IOP of <18 mmHg at any assessment time reached 69%. These figures are higher than those reported for travoprost alone and considerably higher than reported for timolol alone, given twice daily (8). This may be significant since it was demonstrated in the Advanced Glaucoma Intervention Study (AGIS) that those patients who maintained an IOP below 18 mmHg at every measured time exhibited better long-term visual field survival than those who did not (23).

In this study the fixed-dose combination of travoprost 0.004%/timolol 0.5% was safe and well-tolerated when dosed either in the morning or the evening. Relatively few adverse events were reported: the most common treatment-related ocular adverse event was ocular hyperemia, which occurred at an overall incidence of 13.0%. Ocular hyperemia is a class-related adverse effect of the ocular prostaglandin analogues (24) and the incidence in this study was lower than that reported in studies of travoprost alone (7, 8). In only two cases (in one of which ocular hyperemia was combined with ocular edema) did the patient discontinue treatment. In fact when judged on a four-point scale (0 = none to 3 = severe) most cases were judged to be mild to moderate (scores of 1 to 2) in severity and the mean score for ocular hyperemia ranged from 0.35 to 0.65 in the am treatment group and between 0.28 to 0.49 in the pm treatment group.

Ocular use of the non-selective beta-blocker timolol can be accompanied by systemic side effects such as asthma, shortness of breath, bradycardia, and hypotension in susceptible individuals (25, 26). In this study one patient discontinued treatment with the combined product due to a mild attack of asthma but no serious adverse cardiovascular effects were identified. Two patients were diagnosed with hypertension and one with hypotension, but in all cases the condition was not of sufficient concern to interrupt treatment.

Recent large-scale clinical studies, such as the Ocular Hypertension Treatment Study (OHTS) (27), the Early Manifest Glaucoma Trial (EMGT) (28), and AGIS (20), have clearly indicated the significance of lowering IOP in preventing the development of open-angle glaucoma in susceptible individuals and the progression of visual field loss in those who already have the disease. However, these trials have indicated that, to be effective, therapy needs to

reduce IOP as much as possible, commensurate with other factors that affect the general well being and quality of life of the patient. In this study a fixed-dose combination of travoprost 0.004%/timolol 0.5% given once daily was found to produce clinically relevant reductions in IOP from a post-washout baseline (up to 38%) in a group of patients already receiving treatment for open-angle glaucoma or ocular hypertension and the combination was tolerated at least as well as the individual components. This combination product may, therefore, be of value in patients judged to be inadequately controlled on a prostaglandin analogue or ophthalmic beta-blocker alone. Dr Denis was a clinical invstigator on this study and other wise has no financial interest. The others Wells, Andrew and Friren were employees of Alcon at the time the study was conducted.

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