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Adjunctive use of tafluprost with timolol provides additive effects for reduction of intraocular pressure in patients with glaucoma

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PURPOSE. *This study investigated the efficacy and safety of tafluprost as an adjunctive therapy to timolol in patients with open-angle glaucoma or ocular hypertension, uncontrolled by timolol monotherapy.*
METHODS. *This was a randomized, double-masked, parallel-group, multinational and multicenter 12-week phase III study. Tafluprost 0.0015% (once daily: 20:10) or vehicle were administered as adjunctive therapy to timolol 0.5% (twice daily: 08:00 and 20:00) for 6 weeks, after which all patients received tafluprost for 6 weeks. Intraocular pressure (IOP) measurements were conducted at 08:00, 10:00, and 16:00 at baseline, and weeks 2, 4, 6, and 12.*
RESULTS. *A total of 185 patients were randomized to tafluprost (n = 96) or vehicle (n = 89). Reductions in IOP were seen in both groups, which were consistently more pronounced with tafluprost. At week 6, the change from baseline in diurnal IOP ranged from –5.49 to –5.82 mm Hg, and the overall treatment difference (tafluprost vehicle) was –1.49 mmHg (upper 95% confidence interval, –0.66; p<0.001, intention-to-treat population, repeated measurements of the analysis of covariance model). At week 12, the change from baseline ranged from –6.22 to –6.79 mmHg in the tafluprost group. Patients switched from vehicle to tafluprost achieved a similar decrease in IOP to those who received tafluprost throughout the study (group difference at 12 weeks, –0.09 mmHg, p=0.812). There were more ocular adverse events with tafluprost compared with vehicle (42% vs. 29%, respectively), but most were mild in severity.*
CONCLUSIONS. *As adjunctive therapy to timolol, tafluprost achieved a consistently greater reduction in IOP compared with vehicle, and was well tolerated. (Eur J Ophthalmol 2009; 19: 214-22)*

KEY WORDS. *Additive, Adjunctive, Glaucoma, Intraocular pressure, Tafluprost, Timolol*

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INTRODUCTION

Lowering intraocular pressure (IOP) in patients with glaucoma is associated with a decreased disease progression (1, 2). The topical application of a hypotensive agent is first-line treatment for patients with high IOP (3). Historically, beta-blockers, such as timolol, are used to lower IOP (4). Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogues have also demonstrated effective lowering of IOP. Tafluprost is a newly synthesized $PGF_{2\alpha}$ derivative that is a powerful agonist of FP-receptors (5, 6). Through its potent binding activity, tafluprost has demonstrated a reduction in the IOP of both normotensive and hypertensive monkeys (7), and in healthy human volunteers (8), while being generally well tolerated.

In patients with glaucoma or ocular hypertension, not sufficiently controlled with a single agent, a combination of

* see Appendix on pag. 221

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treatments can help in reducing IOP further (4, 9, 10). Timolol and tafluprost have disparate and potentially synergistic mechanisms of action–timolol acts primarily by reducing the production of aqueous humor (11, 12) and tafluprost acts by increasing the uveoscleral outflow (13).
This study investigated the efficacy and safety of tafluprost as an adjunctive therapy to timolol, in patients with open-angle glaucoma or ocular hypertension not controlled by timolol therapy alone.

MATERIALS AND METHODS

Study design

This study was conducted during 2005, at a total of 10 centers: 5 in Russia, 2 in the Ukraine, 2 in Estonia, and 1 in Latvia. Proposals from each center were reviewed and approved by the appropriate Independent Ethics Committees and relevant health authorities in each participating country, according to the national requirements. The study was conducted in accordance with current Good Clinical Practice requirements and the ethical principles of the Declaration of Helsinki. All patients gave verbal and written informed consent.
This was a randomized, double-masked, parallel-group, multinational, and multicenter phase III study. Tafluprost 0.0015% or vehicle eyedrops were administered once daily as adjunctive therapy to timolol 0.5% (twice daily) for 6 weeks. After this period, vehicle drops were switched to tafluprost for the remaining 6 weeks. The total duration of the study for all patients was 12 weeks.

Patients

Prostaglandin-naive patients with primary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma, or ocular hypertension were all eligible for the study. Eligible patients were required to be aged at least 18 years, and were required to have IOP measurements of 22 to 30 mm Hg in at least one eye, for at least one measurement of the diurnal IOP curve (08:00, 10:00, and 16:00) after a 4 week run-in period with timolol. Patients also needed to have a best-corrected Early Treatment Diabetic Retinopathy Study visual acuity score of +0.6 logMAR (Snellen equivalent of 20/80) or better in each eye.
Patients were excluded if they were pregnant or likely to become pregnant, had any uncontrolled systemic diseases (such as hypertension or diabetes), or had any contraindications to beta-blocker therapy. In addition, patients were excluded if they had known allergy or hypersensitivity to any of the study components, had used contact lenses at the first visit or during the study, had any disease or abnormality of the external part of the eye, had an anterior chamber angle of less than 2 according to Schaffer classification, or had an advanced or progressive visual field defect. Patients who had previously participated in a trial using tafluprost, had participated in another drug trial within the previous month, were abusing alcohol or drugs, or who anticipated use of other antiglaucoma medications during the study were excluded.

Treatments

At the screening visit, eligible patients with IOP measurements of 22 to 30 mmHg, who were undergoing monotherapy with treatments other than prostaglandins, started timolol maleate 0.5% eyedrops, dosing twice daily at 08:00 and 20:00 in affected eyes. All other glaucoma medications were discontinued. After a minimum of 4 weeks of treatment with timolol, those patients who still had IOP measurements of 22 to 30 mmHg in at least one eye, in at least one measurement of the diurnal IOP (at 08:00, 10:00, and 16:00), could be enrolled in the study. Patients were randomly assigned to receive one of the following two study medication regimens for 6 weeks: timolol 0.5% twice daily (at 08:00 and 20:00) and tafluprost 0.0015% once daily (20:10) in the affected eyes; or timolol 0.5% twice daily (at 08:00 and 20:00) and vehicle once daily (20:10) in the affected eyes. Thus, timolol 0.5% was an open-label medication, and tafluprost 0.0015% or the vehicle was the masked agent.
For the 6-week extension period, all patients received timolol 0.5% twice daily (at 08:00 and 20:00) and tafluprost 0.0015% once daily (20:10) in the affected eyes. Therefore both timolol and tafluprost were considered open-label medications in the extension period.
If both eyes satisfied the IOP criteria at baseline, then both eyes could be treated with the study medication (tafluprost or vehicle). If only one eye satisfied the criteria, but the other eye also needed to be treated, as judged by the investigator, then both eyes could be treated with the study medication only. All drops were administered in the temporal lower conjunctival culde-sac of the eyes.

Endpoints

The primary efficacy variable was the change from baseline in the overall diurnal IOP after the first 6 weeks. Diurnal IOP measurements were conducted at 08:00, 10:00, and 16:00 at baseline, and weeks 2, 4, 6, and 12. For safety reasons, a single measurement of IOP was taken at 08:00 at week 8, and at the post-study visit. The primary evaluation of IOP was based on the worse eye. If both eyes satisfied the inclusion criteria, then the worse eye was classified as the eye with the higher mean IOP, calculated from the three diurnal IOP measurements (08:00, 10:00, and 16:00) at the baseline visit. If both eyes had the same mean IOP measurements in the diurnal curve, then the right eye was designated as the worse eye.

The secondary efficacy variables for the randomized treatment period were the change from baseline in timewise IOP measurements (08:00, 10:00, and 16:00) at 6 weeks, the change from baseline in the overall diurnal IOP and timewise IOP measurements at 2 and 4 weeks, and the proportion of responders at 6 weeks. A responder was defined as a patient with a specific reduction in IOP measurement, for example 15% reduction with increasing steps of 5%, as compared with baseline or with a specific target IOP value, for example 20 mmHg with decreasing steps of 1 mmHg.

The efficacy variables for the extension period were the change from baseline in the overall diurnal IOP measurements, change from baseline in timewise IOPs (08:00, 10:00, and 16:00), and the proportion of responders, all at 12 weeks.

The safety and tolerability variables studied included adverse events, best-corrected visual acuity, conjunctival redness, biomicroscopy, ophthalmoscopy, a visual field test, iris color, eyelash and eyelid photographs, blood pressure, and heart rate. Adverse events were elicited from the patients at each post-baseline visit. The information included a description of the event, whether or not it was serious, onset and duration, frequency, severity, relation to study treatment, location, action taken, and outcome.

All treated eyes were used in the analysis of ocular safety variables. Conjunctival redness was assessed using a five-point basic scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe). A biomicroscopic examination was conducted at each visit. The examination included evaluation of the eyelids, conjunctiva, cornea, anterior chamber, iris, and lens. The findings were graded from 1 = mild, 2 = moderate, and 3 = severe. Ophthalmoscopy was performed at screening, week 6, and at the post-study visit, and findings were graded as 1 = mild, 2 = moderate, or 3 = severe. A visual field test was carried out at screening, week 6, and the post-study visit, with the results categorized as normal or abnormal; abnormal results were graded as 1 = mild, 2 = moderate, or 3 = severe. Furthermore, the results of the visual field test at week 6 and the post-study visit were compared with the findings at baseline.

Photographs of the iris, eyelashes, and eyelids were taken at baseline, and at weeks 6 and 12. A masked independent evaluator assessed whether there was a clinically significant change from baseline in iris color; eyelash length, density, thickness, or color; and eyelid skin color. Blood pressure and heart rate measurements were taken at screening, baseline, and weeks 6 and 12.

Statistical analyses

The efficacy variables were evaluated using repeated measurements of the analysis of covariance (RM-ANCOVA) and variance (RM-ANOVA) models, and descriptive statistics. The baseline IOP measurement was used as a covariate in the RM-ANCOVA model. For the primary efficacy variable, the superiority of tafluprost compared with the vehicle was evaluated using a 95% confidence interval (95% CI) obtained from the model. Tafluprost was considered superior to the vehicle if the upper limit of the 95% CI (tafluprost-vehicle) did not exceed 0 mmHg (or the corresponding p value was less than or equal to 0.05). Descriptive statistics were employed for the safety variables.

The intention-to-treat (ITT) dataset included all randomized patients who received at least one dose of study treatment and who had at least one efficacy measurement. The per protocol (PP) dataset was the ITT population but excluding those patients or measurements with major protocol violations which were expected to alter the outcome to treatment.

A difference of –2.0 mmHg (tafluprost vs vehicle) was assumed in the sample size calculations. In addition, the following assumptions were made: a standard deviation of 4.0 mmHg for the change in IOP; a two-sided type I error rate of 5%; and a power of 90%. A normal approximation was used in the sample size calculations. This resulted in a sample size of 85 evaluable patients (presuming at least 100 randomized patients) per treatment group.

It was found that eight patients had a large response to

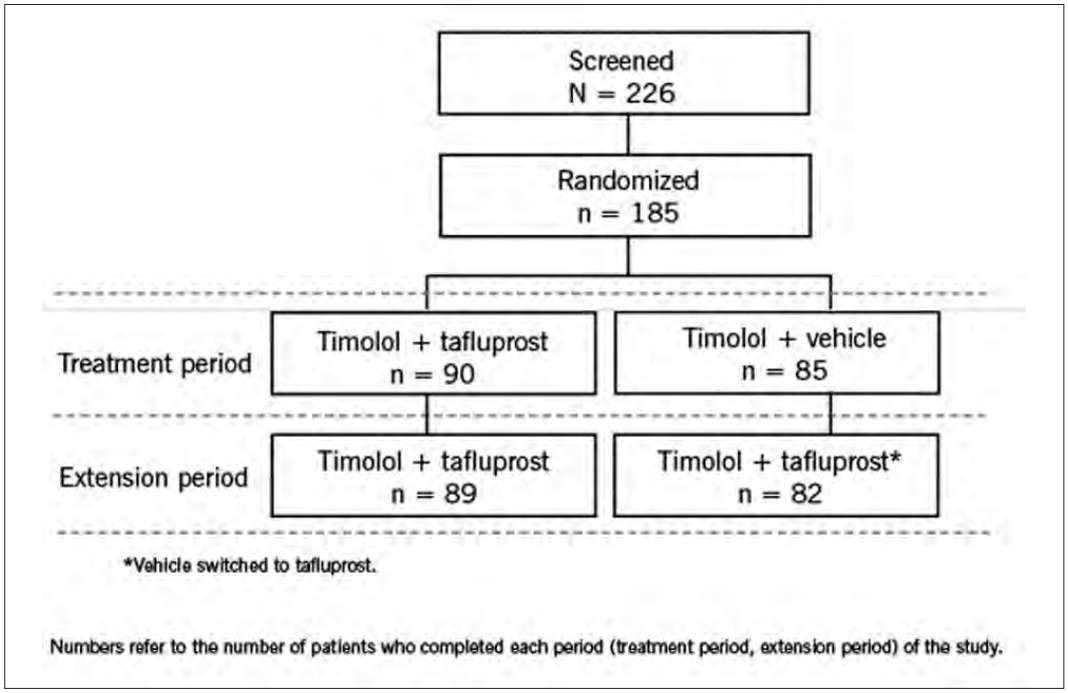

Fig. 1 - *Patient disposition. •N numbers refer to the number of patients who completed each period (treatment period and extension period) of the study.*

vehicle treatment. Therefore, a sensitivity analysis, without eight vehicle responders (IOP levels ≤12 mmHg at 6 weeks), was also performed for the randomized treatment period.

RESULTS

A total of 185 patients were randomized: 96 to timolol plus tafluprost and 89 to the timolol plus vehicle. Of these, 90 and 85 patients, respectively, completed the randomized treatment period, and 89 and 82 patients, respectively, completed the extension phase. Figure 1 illustrates the patient disposition throughout the study.

The mean age of patients in the tafluprost group was 66.3 years (range 39–83) and 68.0 years (range 34–86) in the vehicle group. There were slightly more women than men: 57 (59.4%) in the tafluprost group and 47 (52.8%) in the vehicle group. The majority of patients in both groups had primary open-angle glaucoma (Tab. I).

Efficacy

In patients already receiving timolol therapy, an IOP-lowering effect was seen in both groups during the randomized treatment period (Fig. 2). The effect was clearly and consistently more pronounced in the tafluprost group.

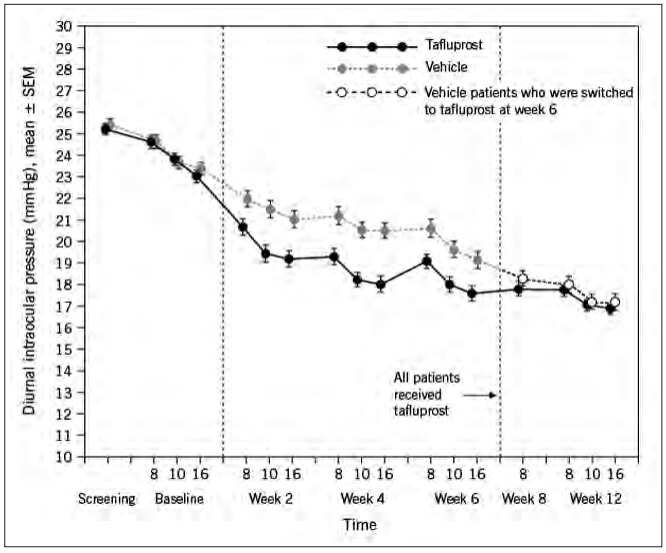

Fig. 2 - *Mean (± standard error of the mean; SEM) diurnal intraocular pressure (IOP) with tafluprost or vehicle, as adjunctive to timolol.*

At week 6, the change from baseline in the tafluprost group ranged from –5.49 to –5.82 mmHg, and the overall treatment difference was –1.49 mmHg (upper 95% CI, –0.66; $p<0.001$, ITT population, RM-ANCOVA model). In the RM-ANCOVA model the upper limit of the CI was less than the predetermined superiority limit of 0 mm Hg, and therefore superiority of tafluprost over vehicle was estab-

lished. Findings from an analysis without the covariate (RM-ANOVA) supported the superiority of tafluprost (treatment difference –1.54 mmHg; upper 95% CI, –0.69; p<0.001, ITT population). Furthermore, results from the PP population were similar and supported the superiority of tafluprost over vehicle.

The superiority of tafluprost was also observed at weeks 2 and 4 at all time points throughout the day (Tab. II). At 6 weeks, the proportion of responders, as assessed by the percentage decrease in mean diurnal IOP, was considerably greater in the tafluprost group compared with the vehicle group (e.g., 26.7% vs 14.1%, respectively, achieved a decline in IOP of ≥30%).

In the extension period (week 6–12), patients in the tafluprost group for the previous 6 weeks achieved a further reduction in IOP; the change from baseline ranged from between –6.22 and –6.79 mmHg at week 12. The patients who switched from vehicle to tafluprost had an estimated mean change of –2.39 mmHg in the overall diurnal IOP measurements (upper 95% CI, –1.89; p<0.001, ITT population, RM-ANCOVA model). Patients who received vehicle eyedrops and then switched to tafluprost reached the same IOP levels as patients randomized to tafluprost treatment from the beginning of the study. This IOP reduction was similar to the reduction seen in those patients treated with tafluprost for the first 6 weeks (treatment difference –0.09 mmHg; upper 95% CI, 0.62; p=0.812, ITT population, RM-ANCOVA model).

A subgroup analysis was performed in which the eight patients who demonstrated a large decline in IOP measurements in the vehicle group were excluded. In this sensitivity analysis, the estimated overall treatment group difference (tafluprost vehicle) at 6 weeks was –2.20 mmHg (upper 95% CI, –1.41; p<0.001, ITT population, RM-ANCOVA model).

Safety

The mean length of exposure was 2.7 months in both groups. During the randomized period, 45% of patients in the tafluprost group and 35% of patients in the vehicle group reported adverse events. One patient experienced a serious nonocular adverse event, which was not related to either treatment (broken leg). Three patients in the

TABLE I - BASELINE PATIENT CHARACTERISTICS (WEEKS 0–6)

Demographic characteristic	Tafluprost (n = 96)	Vehicle (n = 89)
Mean age ± SD (range), y	66.3±8.7 (39–83)	68.0±9.0 (34–86)
Female, n (%)	57 (59.4)	47 (52.8)
Caucasian, n (%)	96 (100)	89 (100)
Mean IOP in worse eye (SD), mmHg		
08:00	24.56 (2.93)	24.56 (2.98)
12:00	23.83 (2.64)	23.61 (2.45)
16:00	23.08 (2.63)	23.31 (2.52)
Ocular diagnosis (all eyes), n (%)		
Primary open-angle glaucoma		
Right eye	78 (81.3)	69 (77.5)
Left eye	78 (81.3)	69 (77.5)
Capsular glaucoma		
Right eye	8 (8.3)	6 (6.7)
Left eye	10 (10.4)	5 (5.6)
Ocular hypertension		
Right eye	3 (3.1)	5 (5.6)
Left eye	3 (3.1)	5 (5.6)
Pigmentary glaucoma		
Right eye	0 (0)	1 (1.1)
Left eye	0 (0)	1 (1.1)
Normal		
Right eye	7 (7.3)	8 (9.0)
Left eye	5 (5.2)	9 (10.1)

SD = standard deviation; IOP = intraocular pressure.

TABLE II - CHANGE IN INTRAOCULAR PRESSURE (IOP) FROM BASELINE THROUGHOUT THE STUDY WITH TAFLUPROST AND VEHICLE

	Change from baseline IOP, mmHg	
	Tafluprost group* (n = 96)	**Vehicle group† (n = 89)**
Week 2		
08:00	–3.94	–2.63
10:00	–4.44	–2.16
16:00	–3.93	–2.32
Week 4		
08:00	–5.25	–3.43
10:00	–5.61	–3.12
16:00	–5.13	–2.80
Week 6		
08:00	–5.49	–4.01
10:00	–5.82	–3.99
16:00	–5.53	–4.15
Week 12		
08:00	–6.79	–6.72‡
10:00	–6.75	–6.44‡
16:00	–6.22	–6.12‡

*Patients in the tafluprost group received tafluprost for the whole study duration (12 weeks).
†Patients in the vehicle group received vehicle for the first 6 weeks and tafluprost for the remaining 6 weeks of the study. Therefore, the data reported for the vehicle group at week 12 (‡) is after 6 weeks of tafluprost therapy.

tafluprost group discontinued the study during the randomized treatment period due to adverse events: two patients had related allergic conjunctivitis (possibly or certainly related to the study medication), and one patient had tinnitus, vertigo, blurred vision, and eye pruritus (possibly related to study medication).

There were fewer nonocular adverse events in the tafluprost group compared with the vehicle group, but the severity and causality was comparable between groups. The ocular adverse events were more common with tafluprost (42%) than with vehicle (29%), but most were mild. The treatment-related ocular adverse events during this period are summarized in Table III. The most common ocular adverse event was conjunctival hyperemia, which was observed in a total of 16% of patients and which was considered to be treatment related in 12% of patients. In the tafluprost group conjunctival hyperemia was mild in 10 patients and moderate in 4 patients. With vehicle, mild and moderate conjunctival hyperemia was observed in 6 and 2 patients, respectively. During the randomized period, there were no changes in iris color or eyelid pigmentation, and only a few signs were seen in the eyelashes with vehicle. In the tafluprost group, mild iris pigmentation was seen in 5–6% of eyes (left or right); mild increased eyelash signs were observed in 17–19% and mild eyelid pigmentation observed in 3–4% of eyes.

During the extension period, the overall rates of adverse

TABLE III - NUMBER OF TREATMENT-RELATED OCULAR ADVERSE EVENTS WITH TAFLUPROST AND VEHICLE DURING THE RANDOMIZED PERIOD (weeks 0–6), BY SEVERITY

Adverse event (MedDRA preferred term)	**Tafluprost (n = 96)**				**Vehicle (n = 89)**			
	Mild	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**Total**
Conjunctival hyperemia	10	4	0	14	6	2	0	8
Conjunctivitis allergic	0	1	1	2	0	0	0	0
Dry eye	2	0	0	2	0	0	0	0
Erythema of eyelid	2	0	0	2	1	0	0	1
Eye irritation	2	1	0	3	1	0	0	1
Eye pruritus	11	2	1	14	0	0	0	0
Growth of eyelashes	1	0	0	1	1	0	0	1
Ocular hyperemia	1	2	0	3	0	0	0	0
Vision blurred	0	1	1	2	0	0	0	0
Visual field defect	0	0	0	0	1	0	0	1
Intraocular pressure increased	0	0	0	0	0	1	0	1

MedDRA = Medical Dictionary for Regulatory Activities.

events were 30% and 35% for the group that received tafluprost for the whole 12-week study duration and patients who were switched from vehicle to tafluprost after week 6, respectively. One patient who switched from vehicle to tafluprost after 6 weeks discontinued during the extension period due to adverse events. The distribution and causality of non-ocular adverse events was comparable between groups during the extension period. As with the randomized period, the most common ocular adverse event was conjunctival hyperemia, which was reported in 13% of patients (data not shown). Overall, there was more eyelash discoloration, thickening, growth, and eyelid hyperpigmentation in the tafluprost group. At week 12, a patient who had switched from vehicle to tafluprost developed mild iris pigmentation in the right eye, another patient had mild eyelid pigmentation on the right eye, and 15–18% of eyes (right or left) had mild eyelash signs. In those patients who continued with tafluprost for the whole 12 weeks, the changes in iris pigmentation, eyelash signs, and eyelid pigmentation were mostly or entirely mild. Overall, changes in iris pigmentation were seen in 5–8% of eyes (right or left), 65–70% of eyes had eyelash signs, and 6–7% of eyes experienced eyelid pigmentation.

One patient in the tafluprost group died as a result of a stroke during the post-study period. However, given the patient's history of arterial hypertension, this was considered unrelated to treatment.

In terms of ocular safety, best-corrected visual acuity remained stable throughout the study in both treatment groups. Most patients had no or mild conjunctival redness. Deteriorations (at least 1 severity score) were mainly seen from week 2 onwards in the tafluprost group, and from week 8 onwards in the vehicle group (2 weeks after switching to tafluprost). There were no clinically significant findings in the other ocular safety variables or in the vital signs.

DISCUSSION

This study investigated the use of tafluprost 0.0015% as an adjunct to timolol in patients only partially controlled with timolol. During the randomized treatment period, an IOP-lowering effect was seen in both treatment groups. This effect was clearly and consistently larger (approximately 2 mmHg) in the tafluprost group compared with vehicle, as shown by both the primary statistical analysis (RM-ANCOVA) and the unadjusted sensitivity analysis (RM-ANOVA). The magnitude of the IOP-lowering effect in the tafluprost group was around –5.5 mmHg at the end of the 6-week randomized treatment period. An even larger change from baseline (around –6.5 mmHg) was seen in the tafluprost group at the end of the extension period, i.e., after 12 weeks of treatment.

The overall treatment difference in this study was comparatively low, possibly due to the IOP reductions seen in the placebo group. The large IOP-lowering potential of placebos has been reported before, most notably in the European Glaucoma Prevention Study (EGPS) (20). This may represent a true placebo effect (20, 21) or could be due to a regression to the mean or selective loss of follow-up patients (22, 23).

Nevertheless, the IOP-lowering effect observed in this study is in line with previous studies investigating the addition of prostaglandin analogues as adjunctive therapy to patients uncontrolled by timolol alone (4, 9, 14-18). While the magnitude of the reduction in IOP varies between studies, when individual studies were combined in a meta-analysis performed by Webers et al, the concomitant use of latanoprost (0.005% once daily) and timolol (0.5% twice daily) resulted in an absolute pooled change from baseline of the mean diurnal IOP curve of –6.0 mmHg (95% CI, –6.8 to –5.2) (24). The magnitude of the IOP-lowering response observed in the current study is therefore comparable with that seen in the previous meta-analysis.

The current study also found that tafluprost, as adjunctive therapy to timolol, was well tolerated, with no unexpected safety findings. Most previous studies investigating the adjunctive use of prostaglandin analogues with beta-blockers have demonstrated that the combination is well tolerated (4, 9, 15, 18, 19). In this current study, there were more adverse events with the active treatment tafluprost compared with vehicle, but most were mild in severity and were known prostaglandin-related adverse events. The increase in eyelash thickening, growth and pigmentation, and eyelid hyperpigmentation observed in the tafluprost group after 12 weeks was probably due to the 6 week longer exposure time to a prostaglandin analogue, when compared with the vehicle group. Only patients who had previously not been exposed to prostaglandin therapy were included in this study. This allowed a more accurate determina-

tion of the incidence of prostaglandin-specific treatment-related adverse events, such as iris pigmentation.
One of the potential limitations of this study was its relatively short-term treatment duration (6 weeks randomized, 12 weeks total). Some previous studies have reported results at 3 months or less (14-16, 18, 19). However, glaucoma is a progressive disease and patients require long-term therapy. Therefore, longer-term studies are required to further establish the efficacy and safety of the adjunctive use of tafluprost and timolol in patients uncontrolled with timolol alone.
In conclusion, this 12-week, randomized, controlled study demonstrated that tafluprost, as adjunctive therapy to timolol, achieves a consistently greater reduction in IOP compared with vehicle, and is well tolerated. Therefore, tafluprost could be considered a suitable add-on therapy for patients with glaucoma and ocular hypertension uncontrolled on timolol alone, who require additional drugs to achieve adequate IOP control.

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