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Efficacy and safety of tafluprost 0.0015% versus latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study

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ABSTRACT.

Purpose: **The objective of the study was to compare the long-term efficacy and safety of tafluprost 0.0015% with latanoprost 0.005% eye drops in patients with open-angle glaucoma or ocular hypertension.**

Methods: **This double-masked, active-controlled, parallel-group, multinational, multicentre, phase III study was conducted at 49 centres in 8 countries. Eligible patients were assigned to treatment administered once daily at 20:00 hrs for up to 24 months. Change from baseline intraocular pressure (IOP) was the primary efficacy variable. Adverse events were recorded and ocular safety was evaluated. Both tafluprost and latanoprost were preserved with benzalkonium chloride.**

Results: **From 533 patients randomized, 402 patients completed 24 months of therapy. Both treatments had a substantial IOP-lowering effect which persisted throughout the study (−7.1 mmHg for tafluprost and −7.7 mmHg for latanoprost at 24 months). Although the IOP-lowering effect during the study was slightly larger with latanoprost, this difference was clinically small and the noninferiority of tafluprost to latanoprost over all diurnal IOP measurements was shown with ANOVA and almost reached with ANCOVA (upper limits of the 95% confidence intervals 1.38 and 1.52 for the overall period, respectively). The noninferiority limit was 1.5 mmHg.**

Conclusions: **Tafluprost is a new effective and well-tolerated treatment for glaucoma and ocular hypertension.**

Key words: glaucoma – intraocular pressure – latanoprost – safety – tafluprost

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Introduction

Elevated intraocular pressure (IOP) is the most important risk factor for developing glaucoma. Reduction of IOP using topical ocular hypotensive agents can prevent or delay the development of open-angle glaucoma (Kass et al. 2002) and slow the progression of glaucoma (The AGIS Investigators: The Advanced Glaucoma Intervention Study (AGIS): 7 2006; Leske et al. 2003). Prostaglandin (PG) analogues are the most potent ocular hypotensive medications for topical use, which is reflected in their use as first-choice therapy for the treatment of open-angle glaucoma and ocular hypertension (European Glaucoma Society 2008). Tafluprost is a new, potent PG analogue with high affinity for the fluoroprostaglandin (FP) receptor ($PGF_{2\alpha}$) (Nakajima et al. 2003; Takagi et al. 2004). Tafluprost lowers IOP in both ocular normotensive and hypertensive monkeys (Takagi et al. 2004). In two phase I randomized, placebo-controlled studies in healthy volunteers, administration of tafluprost eye drops once-daily resulted in a significantly greater reduction in IOP compared with placebo, and tafluprost at a concentra-

tion of 0.005% was significantly more effective than latanoprost in reducing IOP (Sutton et al. 2007, 2008). Tafluprost has also shown an IOP-lowering effect and a good tolerability profile in several shorter term phase II/III studies in patients with glaucoma (Traverso et al. 2006; Hamacher et al. 2008; Egorov & Ropo 2009).

In chronic diseases such as glaucoma, data on sustained efficacy and long-term safety and tolerability are of particular relevance. Therefore, the objective of the present study was to compare the efficacy and safety profile of tafluprost 0.0015% eye drops to latanoprost 0.005% eye drops over 24 months in patients with open-angle glaucoma or ocular hypertension.

Methods

This study was reviewed and approved by appropriate Independent Ethics Committees in each participating country according to national requirements. The study was conducted in accordance with current Good Clinical Practice requirements and the ethical principles of the Declaration of Helsinki. Patients gave informed consent before participating in the study.

Study design

This was a prospective, randomized, double-masked, active-controlled, parallel-group, multinational and multicentre phase III study to compare the efficacy and safety of tafluprost 0.0015% (Santen Ltd, Japan) with latanoprost 0.005% (Xalatan®; Pfizer, New York, NY, USA) eye drops in patients with open-angle glaucoma or ocular hypertension. Both treatments contained the preservative benzalkonium chloride (BAK). Following a washout period determined by the class of any prior antiglaucoma medication (see Table 1), patients were randomly assigned to receive either tafluprost 0.0015% or latanoprost 0.005% eye drops. Randomization was stratified by prior PG use. This was initially a 12-month study, which was later extended to 24 months. This article reports the data after the full 24-month period.

Patients

Patients were eligible if they were ≥18 years old with a diagnosis of primary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma or ocular hypertension, an untreated IOP of 22–34 mmHg in at least one eye (following washout if applicable) and a best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score of +0.6 logMAR (Snellen equivalent of 20/80) or better in each eye. Patients were not eligible if they met any of the prespecified exclusion criteria. A full description of the study inclusion and exclusion criteria are provided in Table 1.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Aged 18 years or more	Females who are pregnant, nursing or planning a pregnancy, or females of childbearing potential who are not using a reliable method of contraception
A diagnosis of open-angle glaucoma (either primary open-angle glaucoma, pigmentary glaucoma or capsular glaucoma) or ocular hypertension.	Previous participation in any clinical trial in which tafluprost was an investigational drug
An untreated (after washout) IOP of 22–34 mmHg in at least one eye at the 8:00 measurement at baseline	Any uncontrolled systemic disease (e.g. hypertension, diabetes)
A best-corrected ETDRS visual acuity score of +0.6 logMAR (Snellen equivalent of 20/80) or better in each eye	Prior filtration surgery or any other ocular (including ocular laser procedures) surgery within 6 months prior to screening in the treated eye(s)
Are willing to follow instructions	IOP ≥34 mmHg at any time-point in either eye at baseline
Have provided a written informed consent	Change of an existing chronic therapy that could substantially effect IOP or the study outcomes ≤30 days prior to screening, or anticipated change in such therapy during the study period
Patients on prior glaucoma medication must have a minimum wash-out as shown below:	Known allergy or hypersensitivity to the study medications or their components, including benzalkonium chloride
≥4 weeks for β-adrenergic antagonists	Use of contact lenses at screening or during the study
≥4 weeks for prostamides or PG analogues	Any active external ocular disease, inflammation, or infection of the eye and/or eyelids within 3 months from the study start
≥3 weeks for α-adrenergic agonists	Any ocular disease/condition that in the opinion of the investigator may place the patient at significant risk or may confound the study results or interfere significantly with the patient's participation in the study
≥7 days for carbonic anhydrase inhibitors	Any corneal abnormality or other condition preventing reliable applanation tonometry
≥5 days for miotics	Anterior chamber angle less than grade 2 according to Schaffer classification as measured by gonioscopy
	Advanced visual field defect
	Patients who cannot safely discontinue use of ocular hypotensive medications during the washout period
	Use of any other antiglaucoma medications than the study medications during the study
	Current alcohol or drug abuse
	Current participation in another clinical trial involving an investigational drug/device or participation in such a trial within the last 30 days

ETDRS = early treatment diabetic retinopathy study; IOP = intraocular pressure; PG = prostaglandin.

Procedures and assessments

A screening visit for all patients included a review of ocular and medical history, measurement of blood pressure (BP) and heart rate (HR), a thorough ophthalmological examination including IOP assessment, visual acuity measurement, biomicroscopy, ophthalmoscopy, gonioscopy, visual field testing, laboratory safety testing and ultrasound evaluation of central corneal thickness. Digital pictures of eyes were taken at baseline visit for subsequent photographic evaluation by a masked independent evaluator of clinically significant changes in iris colour, eyelashes (colour, density, length and thickness) and eyelid colour. Laser flare metre and endothelial cell density assessments were performed at selected centres.

Eligible patients already receiving glaucoma therapy underwent washout prior to a baseline visit during which eligibility was reconfirmed. In addition to the baseline visit, study visits occurred after 2 and 6 weeks, and 3, 6, 9, 12, 12.5–13, 15, 18 and 24 months of therapy. During each of these visits, patients were assessed for changes to prior and concomitant medication, adverse events (AEs), visual acuity, biomicroscopy, conjunctival redness, IOP and compliance. Photographs were taken of eyes and lids using a digital camera for the comparison with the baseline photographs. A listing of all parameters tested and their respective time-points is provided in Table S1.

Tafluprost and latanoprost were packaged in identical bottles and cartons for masking purposes; labelling information provided on the packaging related to study number, patient number, instructions for administration and other relevant information for patients and investigators. Patients were instructed to administer one drop of study medication in the temporal lower cul-de-sac of the affected eye(s) once daily at 20:00 hrs.

End-points

The primary efficacy outcome measure was the change from baseline in the overall diurnal IOP. IOP was determined using the Ocular Hypertension Treatment Study protocol previously described (Gordon & Kass 1997). Diurnal IOP was based on IOP recordings taken at 8:00, 12:00, 16:00 and 20:00. The primary evaluation of IOP was based on the eye with the highest IOP; analysis of IOP was performed at 6 months with a second analysis at 12 months, and sustained-effect analyses of IOP were over the 24 -month period.

Safety and tolerability measures included adverse events, ocular safety (best-corrected visual acuity, conjunctival redness, biomicroscopy, ophthalmoscopical evaluation, visual field test, iris colour/eyelash/lid photographs), overall drop discomfort, systemic (BP and HR) and laboratory safety variables.

Statistical analyses

Efficacy analyses were based on the intent-to-treat (ITT) dataset and the worse eye, and included all randomized patients who received at least one dose of study treatment and had at least one efficacy measurement available. The per-protocol (PP) efficacy dataset was a subset of the ITT efficacy dataset excluding those patients or measures for a given patient with a major protocol violation expected to alter the treatment outcome. In addition, patient data from 3 centres where the proportion of unreturned medication bottles was considerably higher than the average of 12.2% (65.0%, 57.7% and 33.3%) were also excluded from the PP sensitivity dataset. The PP datasets were defined separately for analyses at 6, 12 and 24 months. The safety dataset included all randomized patients who received at least one dose of study treatment and had a subsequent safety measurement.

The primary efficacy end-point was analysed by repeated measurements analysis of covariance (RM ANCOVA). A prespecified sensitivity analysis without baseline IOP as a covariate (RM ANCOVA) was also conducted. The difference between tafluprost and latanoprost was estimated from the RM AN(C)OVA models at 3, 6, 12, 18 and 24 months. A noninferiority limit of 1.5 mmHg was assumed in sample size calculations together with a standard deviation of 4.5 mmHg for the change in IOP, a 2-sided type I error rate of 5%, and a power of 90%. Based on these assumptions, it was determined that a sample size of 190 evaluable patients (240 randomized patients) was required per treatment group. The upper limit of noninferiority was set at 1.5 mmHg as this is the standard acceptance level of noninferiority in glaucoma studies (Strohmaier et al. 1998; Goñi 2005, Diestelhorst & Larsson 2006; Cox et al. 2008).

Results

Patient disposition and demographics

From a total of 631 patients who were screened from 49 centres in 8 countries, 533 patients were randomized to tafluprost (n = 269) or latanoprost (n = 264) between July 2004 and May 2005. Of these, 229 patients in the tafluprost group and 247 patients in the latanoprost group completed the study up to 12 months. A total of 196 patients in the tafluprost group and 224 patients in the latanoprost group continued to the extension period (12–24 months), and 402 patients (185 in tafluprost group and 217 in latanoprost group) completed the full 24-month study period (Fig. 1). PG naïve patients comprised 53% of the enroled patients. There were slightly more patients with prior use of antiglaucoma medication requiring washout in the tafluprost group compared with the latanoprost group (77% versus 73%, respectively).

Patient demographics are summarized in Table 2. Patients in either treatment group were well matched at baseline for age, gender, ethnicity, ocular diagnosis, anterior chamber angle grade, corneal thickness, iris colour, baseline symptoms and prior use of antiglaucoma medication. At baseline, the mean IOP in the worse eye was somewhat higher in the tafluprost group than in the latanoprost group, with a mean diurnal IOP of 24.3 ± 3.0 mmHg and 23.8 ± 2.8 mmHg, respectively.

Efficacy

Both tafluprost and latanoprost had a substantial IOP-lowering effect throughout the study (on average 6–8 and 7–9 mmHg in diurnal time-points, respectively) that was observed by the Week 2 visit and continued up to the Month 24 visit. The baseline 6-, 12- and 24-month mean diurnal IOP findings can be seen in Fig. 2. At the

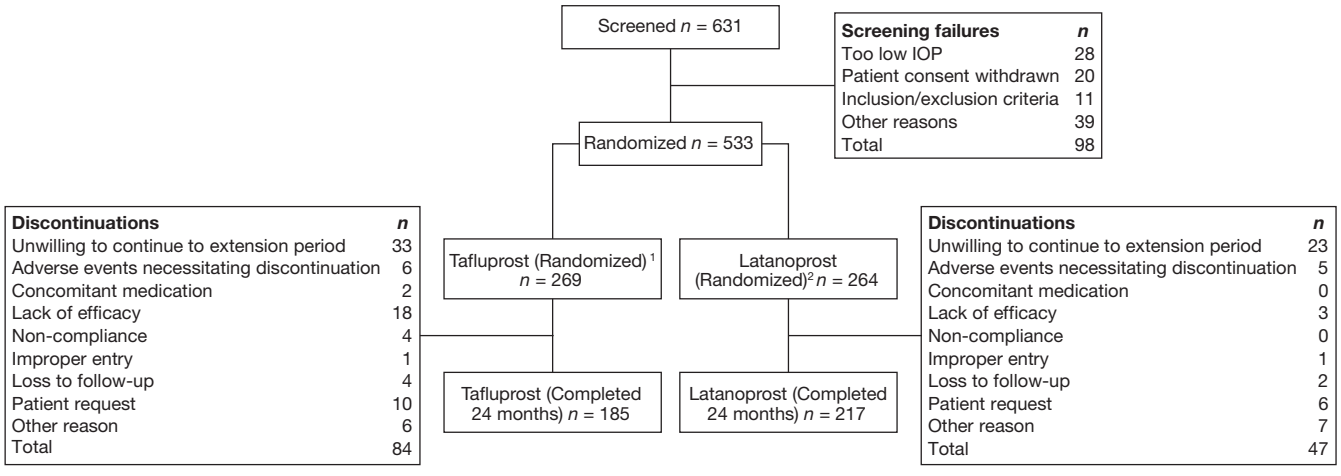

Fig. 1. Patient disposition.

Month 24 visit, the mean decrease in IOP from baseline in the tafluprost group was −7.1 mmHg (29.1%) compared with −7.7 mmHg (32.2%) in the latanoprost group.

The sustained IOP-lowering effect up to 24 months was evaluated using RM ANCOVA and RM ANOVA models for mean diurnal IOP changes at 3, 6, 12, 18 and 24 months. These RM analyses were based on 511 patients who had IOP measurements at 3 months or later, thus providing robust estimates for the treatment difference throughout the study.

The estimated overall treatment difference (tafluprost – latanoprost, ITT population) during the study was 0.95 mmHg with the upper 95% confidence limit of 1.38 (RM ANOVA) and 1.20 mmHg with the upper 95% confidence limit of 1.52 (RM ANCOVA). Thus, noninferiority was shown with ANOVA and almost reached with ANCOVA.

The PP analyses during the study provided similar results as the models for sustained IOP-lowering effect. For instance, the estimate for the treatment difference in the extension PP dataset at 24 months was 0.75 mmHg with ANOVA (upper 95% CI 1.32) and 1.07 mmHg with ANCOVA (upper 95% CI 1.55).

Table 2. Patient demographics.

	Tafluprost (n = 269)	Latanoprost (n = 264)
Mean age, yrs (range)	62.5 (23–86)	62.4 (18–88)
% Female	59.5	57.6
Ethnicity, %		
Caucasian	99.6	99.2
Other	0.4	0.8
Mean corneal thickness, μm (range)	554.9 (422–684)	558.5 (432–672)
Iris colour, n (%)		
Blue/grey	204 (37.9)	210 (39.8)
Brown	158 (29.4)	140 (26.5)
Blue/grey-brown	88 (16.4)	94 (17.8)
Green-brown	56 (10.4)	48 (9.1)
Green	14 (2.6)	16 (3.0)
Yellow-brown	4 (0.7)	8 (1.5)
Other	14 (2.6)	12 (2.3)
Prior antiglaucoma medication, n (%)	207 (77.0)	193 (73.1)
PG analogue	88 (32.7)	85 (32.2)
ß-blocker	79 (29.4)	80 (30.3)
PG and ß-blocker	16 (5.9)	12 (4.5)
α-agonist	3 (1.1)	4 (1.5)
CAIs	21 (7.8)	12 (4.5)

CAIs = carbonic anhydrase inhibitors; PG = Prostaglandin.

Safety

Safety results were analysed from all randomized patients who had received at least one dose of study treatment and had a subsequent safety measurement. A total of 264 patients were eligible for the safety evaluation in each treatment group.

During the complete 24- month study period at least one adverse event was reported by 176 of 264 (66.7%) patients in the tafluprost group compared with 162 of 264 (61.4%) patients in the latanoprost group. A total of 400 ocular adverse events were reported by 127 (48.1%) patients in the tafluprost group compared with 286 ocular adverse events from 117 (44.3%) patients in the latanoprost group. The details of the treatment-related adverse events are listed in Table 3. The ocular adverse events were comparable in terms of type and severity, and there were statistically significant differences between groups (see Table 3). Only 16 ocular adverse events were described as severe (4 related and 5 unrelated for tafluprost, and 3 related and 4 unrelated for latanoprost). Overall drop discomfort was low with approximately 75–80% of patients free from drop discomfort. The distribution of drop discomfort was similar for the two treatment groups (p = 0.402). Neither treatment had any effect on endothelial cell density or laser flare measurements.

A total of 353 nonocular adverse events were reported by 133 (50.4%) patients in the tafluprost group compared with 337 nonocular adverse events in 114 (43.2%) patients in the latanoprost group. Only 11 nonocular

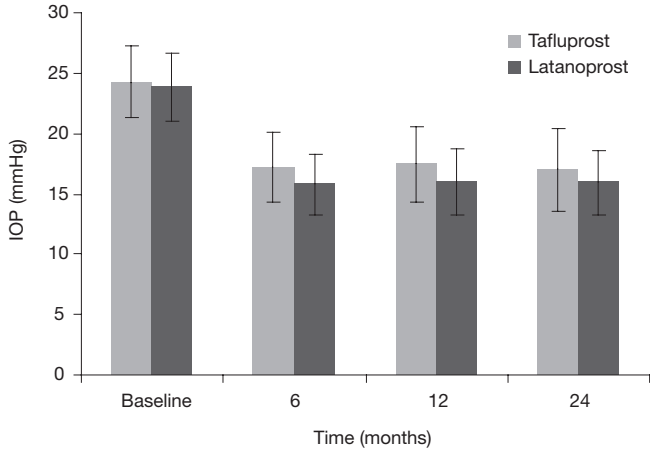

Fig. 2. Mean diurnal intraocular pressure (IOP) at baseline and Months 6, 12 and 24 (bars indicate standard deviation).

adverse events for 8 patients in tafluprost group and 9 events for 7 patients in the latanoprost group were considered treatment related. The distribution of severity and causality for nonocular adverse events was comparable between treatment groups.

Three tafluprost patients and one latanoprost patient experienced serious adverse ocular events, which were judged not related to the study treatment. All other serious adverse events (26 tafluprost, 25 latanoprost) were nonocular and considered not, or unlikely, related to treatment. There were six deaths during the study period, three in each group, none of which was related to study medication.

In general, the LogMAR scores for best-corrected visual acuity remained stable throughout the study in both treatment groups, with few changes from baseline >0.2 LogMAR scores (11.4% in the tafluprost group, 14% in the latanoprost group). Most patients in each group experienced either no or mild conjunctival redness over the study period. Where deterioration (≥1 severity score) did occur, this was mostly observed at Week 2 and was not significantly different between treatment groups. Using reference photographs to assess conjunctival redness over time, at Month 24 there was a mean increase of <0.2 scores on a scale from 0 (normal) to 4 (very severe redness) for both treatment groups ($p = 0.830$) (Fig. 3). Biomicroscopic examinations of the lid, conjunctiva, cornea, anterior chamber, iris and lens for both eyes revealed a limited number of findings of mild severity, mostly seen in the lens, lid and conjunctiva. The findings for tafluprost and latanoprost groups were comparable.

At 24 months, the effect of treatment on eyelashes was absent or mild in >90% of subjects for both tafluprost and latanoprost. Amongst PG naïve patients, there were slightly more cases of severe iris pigmentation in the latanoprost group (Fig. 4), but overall the difference in iris pigmentation between the treatment groups at Month 24 was not statistically significant ($p = 0.848$). There was a slight overall tendency for corneal thinning during the study in both groups, with changes in central corneal thickness (μm) being comparable between those treated with tafluprost (median change −10 [right eye] and −7 [left eye]) and latanoprost (median change −7 [right eye] and −5 [left eye]). There were no significant changes in visual field findings between baseline and 24 months in either treatment group. There were no clinically significant changes in blood pressure or heart rate during the 24- month study period or laboratory parameters up to 12 months.

Discussion

This report presents the first long-term safety and efficacy data for tafluprost in patients with open-angle glaucoma or ocular hypertension. Overall, both tafluprost and latanoprost had a substantial IOP-lowering

Table 3. Most prevalent treatment-related ocular adverse events by severity (treatment causality: possible, probable or certain) (Patient count)*.

	Tafluprost ($n = 264$)				Latanoprost ($n = 264$)				Statistics
Adverse reaction, *n* (%)	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	p Value
Growth of eyelashes	13 (4.8)	4 (1.5)	0	17 (6.4)	8 (3.0)	2 (0.8)	1 (0.4)	11 (4.2)	0.237
Eye irritation	10 (3.8)	4 (1.5)	0	14 (5.3)	11 (4.2)	3 (1.1)	0	14 (5.3)	0.998
Eyelash discolouration	8 (3.0)	5 (1.9)	0	13 (4.8)	7 (2.7)	3 (1.1)	0	10 (3.8)	0.531
Eye pain	11 (4.2)	4 (1.5)	0	15 (5.6)	6 (2.3)	1 (0.4)	0	7 (2.7)	0.058
Ocular hyperaemia	8 (3.0)	5 (1.9)	1 (0.4)	14 (5.3)	4 (1.5)	3 (1.1)	0	7 (2.7)	0.172
Cataract†	2 (0.8)	6 (2.3)	0	8 (3.0)	4 (1.5)	5 (1.9)	1 (0.4)	10 (3.8)	0.333
Conjunctival hyperaemia	9 (3.4)	2 (0.8)	0	11 (4.2)	4 (1.5)	0	0	4 (1.5)	0.073
Dry eye	4 (1.5)	3 (1.1)	0	7 (2.7)	5 (1.9)	0	0	5 (1.9)	0.531
Eye pruritus	6 (2.3)	0	0	6 (2.3)	3 (1.1)	0	0	3 (1.1)	0.339
Eyelash thickening	2 (0.8)	3 (1.1)	0	5 (1.9)	1 (0.4)	3 (1.1)	0	4 (1.5)	0.756
Eyelid oedema	2 (0.8)	3 (1.1)	0	5 (1.9)	2 (0.8)	2 (0.8)	0	4 (1.5)	0.803
Iris hyperpigmentation	3 (1.1)	1 (0.4)	0	4 (1.5)	2 (0.8)	2 (0.8)	0	4 (1.5)	0.97
Visual field defect	3 (1.1)	2 (0.8)	0	5 (1.9)	2 (0.8)	1 (0.4)	0	3 (1.1)	0.576
Foreign-body sensation	2 (0.8)	0	0	2 (0.8)	4 (1.5)	0	1 (0.4)	5 (1.9)	0.234

* Reported for more than five patients.
† Includes cortical, nuclear and subcapsular cataracts.

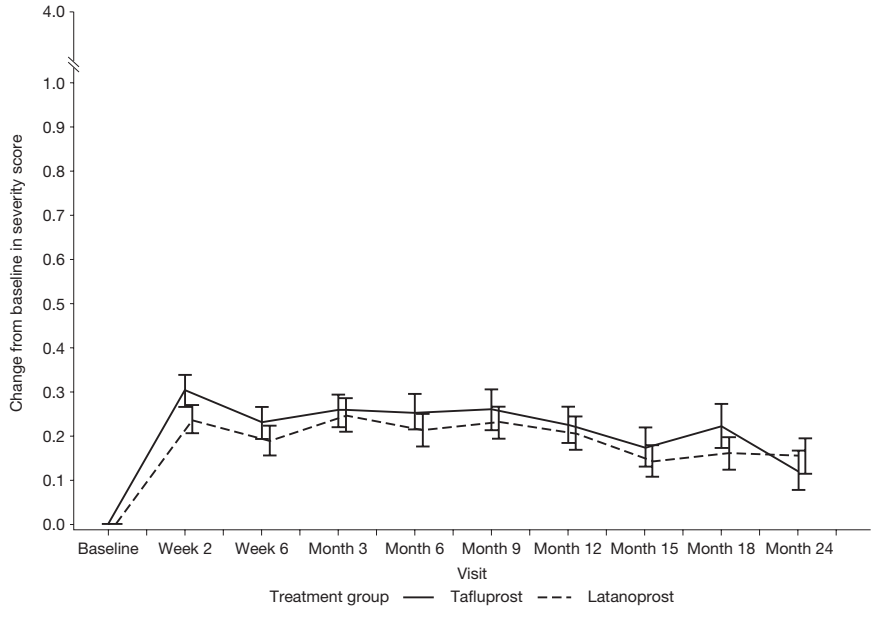

Fig. 3. Mean of largest deterioration in conjunctival redness from baseline in severity score (bars indicate standard error of the mean).

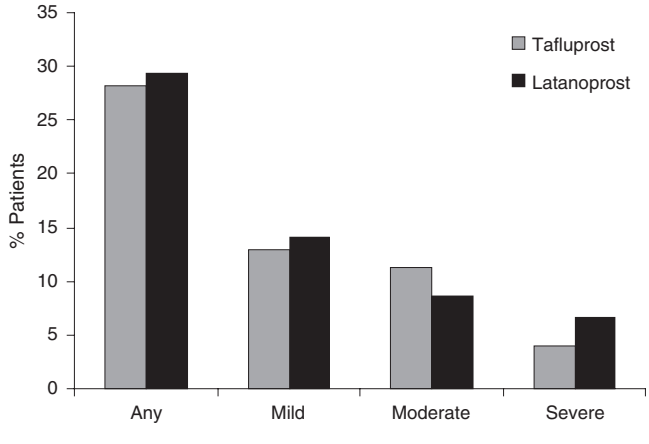

Fig. 4. Increased iris pigmentation by severity in prostaglandin naïve patients at 24 months (mean percentage of treated eyes compared against baseline photographs).

effect that was sustained throughout the 24 month study period. At 24 months, the mean decrease in diurnal IOP from baseline was −7.1 mmHg in the tafluprost group and −7.7 mmHg in the latanoprost group. Although the IOP-lowering effect during the study was slightly larger with latanoprost, this difference was clinically small. Furthermore, the upper limits of the 95% confidence intervals for the overall treatment difference were 1.52 (ANCOVA) and 1.38 (ANOVA) from the RM models for diurnal IOP changes over the study. As the noninferiority rate was based on 1.5 mmHg, noninferiority of tafluprost was shown with ANOVA and almost reached with ANCOVA.

The discontinuation rates were low in both groups. There is a statistically significant difference in the lack of efficacy discontinuation rates in favour of latanoprost (13 versus 3, $p = 0.01$, Fisher's exact test), all other reasons for discontinuations were comparable between groups. This effect appeared dependent on prior combination therapy with 6 out of 13, and 2 out of 3, tafluprost and latanoprost patients, respectively, who discontinued because of the lack of efficacy previously requiring PGs and ß-blocker therapy before enroling in the trial. In total there were more patients in the tafluprost group using PGs and ß-blockers concurrently as a prior medication than in the tafluprost group (16 versus 12). This suggests that there were more treatment-resistant patients in the tafluprost group, possibly reflected in the higher baseline IOP in the tafluprost group (0.43 mmHg on average).

Trials investigating the PG analogues are typically of short duration. In analysing the literature on glaucoma therapy, Lee et al. reported that the median study duration for the PG analogues was 12 weeks and 78% of trials had a duration of ≤3 months (Lee et al. 2008). However, as glaucoma therapy is given indefinitely, lengthier studies are required to determine the effects of glaucoma therapies in the long term, both with regards to efficacy and tolerability. In this study, latanoprost and tafluprost both achieved a substantial and sustained IOP-lowering effect which was maintained over the full 24 month study period. The reduction in IOP from baseline seen with latanoprost at 24 months observed in this study is similar to (Watson 1998; Alm & Widengård 2000; Hedman et al. 2002) or larger than (van der Valk et al. 2005) reported in previous studies. The results from two meta-analyses indicate that the PGs possess similar IOP-lowering efficacy (van der Valk et al. 2005; Eyawo et al. 2009). In a meta-analysis by van der Valk et al., IOP reduction between the three currently available prostanoids was similar (latanoprost 28–31%, bimatoprost 28–33% and travoprost 29–31% from the baseline) (van der Valk et al. 2005). The IOP reductions seen with tafluprost (27–31% from baseline) and latanoprost (29–35% from baseline) in this study are in line with those other members of the PG class (van der Valk et al. 2005).

This study included a comprehensive safety analysis and found no unexpected adverse events associated with long-term tafluprost treatment. Both study drugs were well tolerated and as expected for this type of PG analogues. Overall, approximately 65% of the patients in each treatment group reported adverse events which were predominantly mild to moderate in severity. Conjunctival hyperaemia was the most frequently reported

side-effect in the present study. Consistent with this finding, hyperaemia is the most commonly reported local side-effect of the PG analogues, with an incidence rate of 5–20% with latanoprost, 35–50% with travoprost, and 15–55% with bimatoprost at 12 weeks (Parrish et al. 2003). Studies have indicated that hyperaemia negatively affects patient compliance and persistency with the PG analogues (Feldman 2003; Reardon et al. 2003). In the current study, tafluprost and latanoprost were associated with similar rates of conjunctival or ocular redness, and the overall rates were low with only 7.4% of patients reporting an adverse event of ocular or conjunctival hyperaemia during the study period. The severity of conjunctival hyperaemia, assessed by detailed photographic evaluations, was also similar between both study drugs with mean hyperaemia scores ranging from 0.13 to 0.31 with tafluprost and 0.15 to 0.24 with latanoprost. These scores are slightly lower than those reported in other trials with latanoprost (mean hyperaemia scores 0.4–0.5) (Alm & Stjernschantz 1995; Camras 1996, Watson & Stjernschantz 1996). If conjunctival and ocular hyperaemia are grouped together, the overall incidence was 9.1% in the tafluprost group compared with 5.7% in the latanoprost group ($p = 0.033$). In addition to hyperaemia, the changes from baseline in other safety assessments were similar between the two groups.

The use of $PGF_{2\alpha}$ analogues is associated with a localized increase in pigmentation levels that can result in darkening of the eyelashes, eyelids and the iris (Alm et al. 2008, Cracknell & Grierson 2009). Whilst these changes are thought to be largely cosmetic in nature, in contrast to the darkening of the eyelashes and eyelids which are reversible upon cessation of therapy, an increase in iridial pigmentation levels is thought to be permanent. This effect is mostly mild, with only 10% of patients able to detect colour changes after 3 years of latanoprost therapy (Stjernschantz et al. 2002). Iridial darkening appears dependent on the initial eye colour with uniform and blue/grey eyes largely unaffected and heterochromic and/or hazel eyes at the highest risk (Alm et al. 2008; Cracknell & Grierson 2009). The effect is proportional to length of therapy and in a 5-year study of patients receiving adjunctive latanoprost, 94% of patients who experienced iris darkening did so within the first 24 months of therapy (Alm et al. 2004). As such the rates of iris darkening seen in the present study should provide a good estimate of 'real-world' incidence. Amongst PG naïve patients in the present study, increased iris pigmentation at 24 months was observed in 28.0% of latanoprost-treated eyes and 26.1% of tafluprost-treated eyes. These values are similar to the rates observed in the study by Alm et al. where 31.3% of patients experienced increased iris pigmentation at 24 months (Alm et al. 2004).

Of note, both treatments used in this study contained preservatives. The use of preservatives results in numerous adverse effects to the ocular surface (Baudouin 2008), and preservative-free formulations are associated with significantly reduced adverse reactions, such as hyperaemia and dry eye sensation, and improved the patient tolerance to therapy (Jaenen et al. 2007). A preservative-free formulation of tafluprost is available and studies have demonstrated that the preservative-free formulation of tafluprost has an equivalent pharmacokinetic and efficacy profile to its preserved counterpart (Hamacher et al. 2008; Uusitalo et al. 2008).

In conclusion, this 24-month phase III study showed that both tafluprost and latanoprost yielded a substantial reduction in IOP which was sustained for 24 months. Conjunctival redness was either absent or mild, and demonstrated similar progression for the two treatment groups. Tafluprost can therefore be considered an option for the treatment of patients with open-angle glaucoma or ocular hypertension.

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Supporting information

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Table S1. Schedule for safety examinations.

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