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Efficacy and safety levels of preserved and preservative-free tafluprost are equivalent in patients with glaucoma or ocular hypertension: results from a pharmacodynamics analysis

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ABSTRACT.

Purpose: **Tafluprost is a new prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) derivative in development for the treatment of glaucoma. Tafluprost is the first $PGF_{2\alpha}$ analogue with a preservative-free formulation.**

Methods: **This randomized, investigator-masked, multicentre, crossover phase III study evaluated the pharmacodynamics and safety of preserved and preservative-free tafluprost 0.0015% eyedrops administered for 4 weeks in 43 patients with open-angle glaucoma or ocular hypertension. The primary variable was change from baseline in overall diurnal intraocular pressure (IOP) at 4 weeks. Adverse events and other safety parameters were also analysed.**

Results: **Decreased IOP was clearly observed with both formulations at week 1 and was sustained until week 4. The overall treatment difference (preservative-free versus preserved formulations) at week 4 was 0.01 mmHg (95% confidence interval − 0.46 to 0.49; p = 0.96). There were no unexpected safety-related findings. Both formulations were well tolerated and most adverse events were ocular and mild in severity.**

Conclusions: **The reduction in IOP achieved by preservative-free tafluprost is equivalent to that obtained with the preserved formulation. The preservative-free formulation was generally well tolerated.**

Key words: benzalkonium chloride – glaucoma – intraocular pressure – preservative-free – tafluprost

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Introduction

Glaucoma is often associated with elevated intraocular pressure (IOP) which, if untreated, can lead to damage of the optic nerve and loss of vision. Reducing IOP can slow the progression of disease in patients with glaucoma (AGIS Investigators 2000; Leske et al. 2003), and normalizing IOP in patients with ocular hypertension can delay or even prevent the development of open-angle glaucoma (Kass et al. 2002).

Topical ocular hypotensive medications are prescribed to lower IOP in patients with glaucoma or ocular hypertension. β-blockers (e.g. timolol) are used as first-line therapy, but are associated with systemic side-effects (e.g. bradycardia, fatigue, depression). Analogues of prostaglandins have proved effective at lowering IOP without causing systemic side-effects. The prostaglandin analogues latanoprost, bimatoprost and travoprost are currently available as topical antiglaucoma agents, and are recommended by the European Glaucoma Society Guidelines (2008) as first-line therapy for lowering IOP in glaucoma.

Preservatives, such as benzalkonium chloride (BAC), are used to keep topical solutions sterile. However, several studies have reported that in some cases the use of preservatives in antiglaucoma medications is associated with an increased incidence of adverse effects on the ocular surfaces. These include goblet cell loss (Steuhl et al. 1991), increased subepithelial collagen deposition (Schwab et al. 1992), and infiltration of the substantia propria by inflammatory cells (Broadway et al. 1993, 1994; Baudouin et al. 1999). Furthermore, the use of preserved therapies in patients with glaucoma increases reports of signs and symptoms on the ocular surface, including dry eye and irritation (Furrer et al. 2002; Pisella et al. 2002; Mundorf et al. 2003; Jaenen et al. 2007).

Tafluprost (AFP-168) is a newly synthesized prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogue in clinical development. During animal studies, tafluprost demonstrated more potent fluoroprostaglandin (FP)-receptor binding than latanoprost (Nakajima et al. 2003; Ota et al. 2005), and reduced IOP in both normotensive and hypertensive monkeys (Takagi et al. 2004). In healthy human volunteers, tafluprost also reduced IOP to a greater extent than latanoprost and was well tolerated (Sutton et al. 2007). A preservative-free formulation of tafluprost 0.0015% has been developed. It represents the first preservative-free formulation of a $PGF_{2\alpha}$ analogue preparation. This phase III clinical study was carried out to compare the efficacy and safety levels of preserved and preservative-free tafluprost 0.0015% eyedrops in patients with either open-angle glaucoma or ocular hypertension.

Materials and Methods

Study design

The study was conducted at two centres in Germany and one in Finland. The appropriate independent ethics committees approved the study protocol. The study was conducted according to the guidelines of the Declaration of Helsinki and all patients gave written informed consent before participating.

The study was a randomized, investigator-masked, multicentre, crossover phase III trial of two formulations of tafluprost 0.0015% eyedrops (Taflotan®; Santen Oy, Helsinki, Finland), with or without the preservative BAC (FeF chemicals A/S, Køge, Denmark) 0.1 mg/ml, in patients with either open-angle glaucoma or ocular hypertension.

The study consisted of two treatment periods. Patients were treated with either the preserved formulation of tafluprost 0.0015% once/day for 4 weeks and then switched to the preservative-free formulation for a further 4 weeks, or they were treated with the preservative-free formulation of tafluprost 0.0015% once/day for 4 weeks and then switched to the preserved formulation for the remaining 4 weeks (Fig. 1).

Patients who met the criteria for enrolment at the screening visit entered a washout period prior to the randomization and baseline visit (visit 1). The minimum washout periods were: 4 weeks for patients previously treated with β-adrenergic receptor agonists (β-blockers); 4 weeks for patients using prostamides or prostaglandin analogues; 3 weeks for patients using α-adrenergic receptor agonists (α-agonists); 7 days for patients using carbonic anhydrase inhibitors, and 5 days for patients using miotics. If considered necessary, the carbonic anhydrase inhibitor brinzolamide twice/day was allowed as a run-in medication (brinzolamide had to be stopped at least 7 days prior to the end of the necessary washout period). The second washout phase lasted a minimum of 4 weeks.

Patients

Patients of either sex and any race were eligible for the study. Inclusion criteria required participants to be aged ≥ 18 years, willing and able to follow instructions, have a diagnosis of open-angle glaucoma, capsular glaucoma, pigmentary glaucoma, or ocular hypertension, and have prior use of topical prostaglandins with a documented positive treatment response (15% reduction in IOP). Patients were also required to have an untreated (after washout) IOP of 22–34 mmHg in at least one eye at the 08.00 hours measurement, and a best corrected Early Treatment

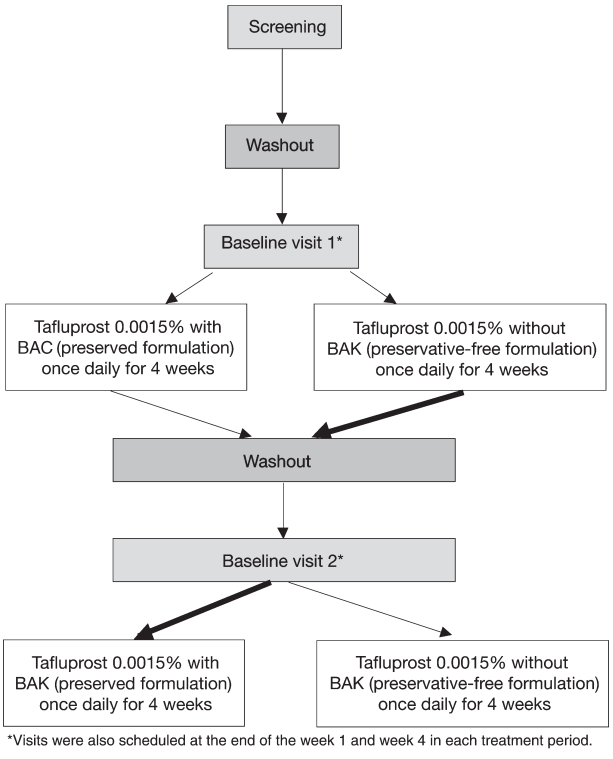

Fig. 1. Study design: a randomized, crossover, multicentre study. The thick line indicates the crossover nature of the study: patients who received tafluprost without benzalkonium chloride (BAC) for the first treatment phase, received tafluprost with BAC during the second treatment phase (and vice versa).

Diabetic Retinopathy Study (ETDRS) visual acuity (VA) score ≥ 0.6 log-MAR in each eye.

Patients were excluded from the study if they had IOP > 34 mmHg in either eye at baseline visit 1, or had a known allergy or hypersensitivity to any of the study medications or constituents, including BAC. Other exclusion criteria were: use of contact lenses at screening or during the study; prior filtration surgery or other ocular surgical procedures within 6 months; any condition preventing reliable applanation tonometry; any advanced visual field defect; any active external ocular disease; inflammation or infection of the eye and/or eyelids within 3 months, and any ocular presence of any uncontrolled systemic disease. Women of childbearing age were not allowed to participate in the study if they were using an unreliable form of contraception, planning a pregnancy, were pregnant or were breast-feeding. Patients were not allowed to enter the study if they had previously participated in any study in which tafluprost was the investigational drug.

Procedures

Patients were randomized to one of the two treatment sequences (Fig. 1) at baseline visit 1. The randomization was stratified by study centre and carried out using randomly permuted blocks in order to ensure a balanced number of patients in the treatment sequences throughout the study.

After randomization, patients were instructed to administer one drop of the study medication into each affected eye, once/day at 20.00 hours. No concomitant systemic medications that might induce any change in IOP were to be initiated during the study period and no changes were to be made to the dosage of any current medications. Intraocular pressure was measured using applanation tonometry at the screening visit and at 08.00, 12.00, 16.00 and 20.00 hours at the baseline, week 1 and week 4 visits of each of the study periods.

End-points

The primary pharmacodynamic endpoint in the study was the change in overall diurnal IOP from baseline to week 4. Secondary pharmacodynamic variables were changes from baseline IOP at each of the timed measurements (08.00, 12.00, 16.00, and 20.00 hours) at week 4, and changes from baseline in overall diurnal IOPs and timed IOP measurements at week 1.

Adverse events and other safety variables were also evaluated. All adverse events were recorded with details of the type of adverse event, onset and duration, severity, frequency, probable relationship to study medication, location (right, left or both eyes), action taken and outcome. Ocular and non-ocular adverse events were recorded separately. Other ocular safety examinations were carried out and the results recorded. These included: best corrected VA (BCVA); biomicroscopy of the eyelids, conjunctiva, cornea, anterior chamber, iris and lens; ophthalmoscopic assessment, and visual field test.

Statistical methods

Pharmacodynamics

The primary evaluation of the pharmacodynamic variables was carried out on the efficacy data from the intention-to-treat (ITT) population and the per-protocol (PP) population. The primary statistical analysis was performed on the data from the eye with the higher IOP at 08.00 hours at baseline visit 1. Results based on the mean of the treated and eligible eyes were summarized descriptively.

A repeated measures (RM) analysis of covariance (ANCOVA) model and descriptive statistics were used to analyse changes from baseline in diurnal IOP at week 4. The RM ANCOVA model included fixed effects for baseline, sequence, period, treatment, time, sequence by time, period by time, and treatment by time. Differences between the preserved and preservative-free formulations of tafluprost were evaluated using two-sided 95% confidence intervals (95% CIs), which were estimated from the RM ANCOVA model using a contrast over all four timed IOP assessments. Equivalence was determined if the 95% CI around the treatment difference was within ± 1.5 mmHg. This is a standard acceptance interval used in non-inferiority and equivalence determinations in glaucoma studies.

Secondary pharmacodynamic analysis of the four timed IOP measurements (08.00, 12.00, 16.00 and 20.00 hours) at week 4 were also carried out using the RM ANCOVA model. Overall and timed comparisons of IOP measurements at week 1 were conducted using a similar ANCOVA model.

The target sample size for the study was 34 evaluable patients (40 randomized), assuming a standard deviation (SD) of 3.0 mmHg change in IOP, a power of 80%, an intra-class correlation coefficient of 0.60 and a two-sided type 1 error rate of 5%.

Safety

All ocular and non-ocular adverse events were tabulated by system organ class, preferred term, causality and severity, and analysed by descriptive summary. The McNemar test was used for comparison of the most prevalent adverse events. Ocular safety variables (BCVA, biomicroscopy and ophthalmoscopy findings, and visual field test) were summarized descriptively for all treated eyes.

Results

Patients

A total of 43 patients were randomized into the study; the ITT population included all 43 patients. The PP population included 41 patients: one patient was excluded because of a major protocol violation (variation of > 3 hours in time of administration of medication), and one patient withdrew from the study as a result of lack of efficacy. Baseline patient demographics are summarized in Table 1. The mean age of the patients was 65.3 years (range 35–85 years). There were 16 men and 27 women in the study. All patients were White. On study entry, approximately 60% of patients had primary open-angle glaucoma and slightly over 30% of patients had ocular hypertension. Mean central corneal thickness was 548.7 μm (range 476–662 μm) in the right eye and 547.0 μm (range 469–662 μm) in the left eye.

Pharmacodynamics

At baseline, mean (SD) IOP measurements were comparable between preserved and preservative-free formulations. Mean (± SD) IOP measurements during the study are shown in Fig. 2.

Table 1. Baseline patient characteristics (n = 43).

Characteristic	n	Percentage
Sex		
Male	16	37.2
Female	27	62.8
Iris colour		
Blue–grey	17	39.5
Brown	13	30.2
Green–brown	6	14.0
Blue–grey–brown	4	9.3
Green	2	4.7
Other	1	2.3
Primary diagnosis		
Open-angle glaucoma		
Right eye	26	60.5
Left eye	28	65.1
Capsular glaucoma		
Right eye	3	7.0
Left eye	1	2.3
Ocular hypertension		
Right eye	14	32.6
Left eye	13	30.2
Normal		
Right eye	0	0
Left eye	1	2.3

Table 2. Treatment group differences (preservative-free versus preserved formulations) in post-baseline intraocular measurements at each time-point for weeks 1 and 4.

	Treatment group difference (95% CI), mmHg	p-value
Week 1		
08.00 hours	− 0.32 (− 0.96 to 0.32)	0.32
12.00 hours	− 0.25 (− 0.89 to 0.40)	0.45
16.00 hours	− 0.39 (− 1.03 to 0.26)	0.24
20.00 hours	− 0.13 (− 0.77 to 0.52)	0.70
Week 4		
08.00 hours	0.24 (− 0.51 to 0.98)	0.53
12.00 hours	0.11 (− 0.64 to 0.86)	0.77
16.00 hours	0.00 (− 0.74 to 0.75)	1.00
20.00 hours	− 0.30 (− 1.04 to 0.45)	0.43

Intention-to-treat population, repeated measures ANCOVA model.
95% CI = 95% confidence interval.

Similar reductions in IOP of > 5 mmHg were clearly seen with the preservative-free and preserved formulations by week 1.

This IOP-lowering effect was sustained and similar with both formulations at week 4. In the RM ANCOVA analysis on the ITT population (n = 43), the estimated overall treatment difference between the preservative-free and preserved formulations was 0.01 mmHg (95% CI − 0.46 to 0.49; p = 0.96). The 95% CI was within the equivalence range of ± 1.5 mmHg. Corresponding analysis on the PP population (n = 41) showed a treatment difference at week 4 of − 0.05 mmHg (95% CI − 0.52 to 0.42; p = 0.83), confirming the results of the ITT analysis and the equivalence of treatments.

Secondary efficacy analyses were performed on the timed comparisons of IOP at weeks 1 and 4. Comparisons between formulations showed similar results to the overall diurnal IOP comparison at all time-points (Table 2).

Sensitivity analyses of the primary and secondary efficacy data, without the baseline IOP values as a covariate (i.e. RM ANOVA analyses), confirmed the results of the RM ANCOVA equivalence testing. In this case, the difference (preservative-free versus preserved) was − 0.12 mmHg (95% CI − 0.95 to 0.71; p = 0.77) in the ITT analysis.

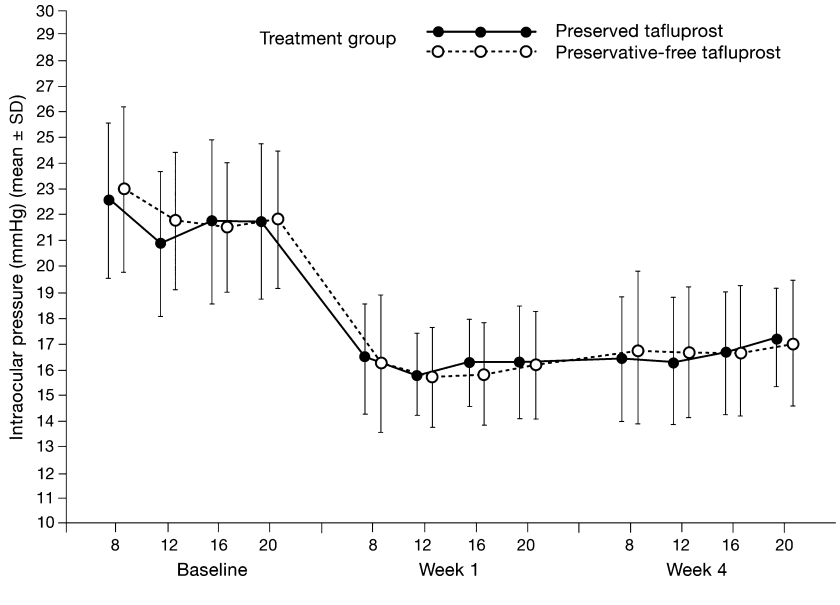

Fig. 2. Mean (± standard deviation) intraocular pressure (IOP) in the preserved and preservative-free tafluprost formulation treatment groups. SD = standard deviation.

Safety

Mean lengths of exposure to the preserved and preservative-free formulations of tafluprost 0.0015% were similar (28.0 days for the preserved formulation, 28.4 days for the preservative-free formulation). Overall, both tafluprost formulations were well tolerated and most adverse events were ocular and mild in severity. Treatment-related ocular adverse events with preserved and preservative-free tafluprost formulations are shown in Table 3. There were no serious adverse events and no withdrawals caused by adverse events in this study.

A total of 11 (25.6%) patients who received the preservative-free formulation and seven (16.7%) patients who received the preserved formulation experienced adverse events. Of the 31 adverse events reported, 27 (87.1%) were ocular and four (12.9%) non-ocular. Slightly more ocular adverse events were reported for the preservative-free formulation compared with the preserved formulation. The most commonly reported adverse event in both groups was conjunctival hyperaemia. Conjunctival hyperaemia was observed in a total of eight patients, of whom two had received preserved tafluprost and six had received preservative-free tafluprost (p = 0.125). Four non-ocular adverse events were reported, one with preservative-free treatment and three with preserved

Table 3. Treatment-related ocular adverse events with preserved and preservative-free tafluprost.

Ocular adverse event	Preserved tafluprost (n = 42)	Preservative-free tafluprost (n = 43)
Conjunctival hyperaemia	2	6
Erythema of eyelid	1	1
Eye pruritus	1	1
Foreign body sensation in eyes	1	1
Ocular hyperaemia	0	2
Anterior chamber cells	0	1
Blepharitis	0	1
Eye pain	0	1
Increased lacrimation	0	1
Punctate keratitis	0	1
Blurred vision	1	0

treatment. None of the non-ocular adverse events were considered to be treatment-related.

In terms of ocular safety, BCVA remained stable throughout the study for both formulations. Changes from baseline of > 0.2 logMAR units were observed in three patients, of whom two had received the preservative-free formulation and showed a slight improvement, and one had received preserved tafluprost and had a slight worsening. The majority of biomicroscopic findings in the lens, conjunctiva, lids and cornea were present at the start of the study and were mild in severity. Ophthalmoscopy revealed only a few changes in the vitreous humour, retina and optic nerve during the study period. A total of four patients had clinically significant changes in the visual field (mild worsening in three, improvement in one). Overall, there were no unexpected changes in ocular safety variables.

Discussion

The results of this study confirm that preserved and preservative-free formulations of tafluprost 0.0015% achieve equivalent decreases in IOP in patients with glaucoma or ocular hypertension. Both the preserved and preservative-free formulations of tafluprost achieved a clear reduction in IOP within 1 week. This IOP reduction was sustained at week 4 with both treatments and the IOP decreases were equivalent between the two formulations. The treatment group difference (preservative-free tafluprost versus preserved tafluprost) at week 4 was 0.01 mmHg (95% CI − 0.46 to 0.49; p = 0.96) in the ITT population.

Similar effects in terms of lowering IOP with preserved and preservative-free tafluprost 0.0015% eyedrops were shown in a pharmacokinetic study performed with healthy volunteers (Uusitalo et al. 2008). Taken together, these studies suggest that removing the preservative BAC from the tafluprost formulation does not affect its ability to lower IOP in either healthy volunteers or patients with glaucoma.

The present study shows that both preserved and preservative-free formulations of tafluprost 0.0015% are well tolerated in patients with glaucoma. There were no serious adverse events or adverse event-related study withdrawals. Adverse events with both formulations were mostly ocular and mild in severity. In this study, incidences of conjunctival hyperaemia were reported more often by patients using the preservative-free tafluprost formulation than the preserved formulation. It should be noted that in the study investigating the pharmacokinetics of tafluprost in healthy volunteers, comparable rates of conjunctival hyperaemia were reported for both the preservative-free and preserved formulations (Uusitalo et al. 2008). However, the conjunctival hyperaemia was mostly of moderate severity with preserved tafluprost, and of mild severity with preservative-free tafluprost (Uusitalo et al. 2008). Thus, overall in both studies, preservative-free tafluprost was well tolerated and resulted in no unexpected adverse events.

Up to 34% of patients with glaucoma aged > 65 years suffer from dry eyes (Smith et al. 2007). The impaired tear film in these patients may reduce the resistance of the conjunctiva or cornea to potential irritants. These patients would, therefore, be most susceptible to the effects of preservatives. Furthermore, > 50% of patients treated with prostaglandin analogues prematurely discontinue their medication. Patients who identified adverse events as a 'significant problem' were most likely to have poor adherence (Zimmerman et al. 2007). Another study showed that administration of a preservative-free solution resulted in fewer ocular signs and symptoms (Jaenen et al. 2007). Therefore, it seems that preservative-free formulations would be beneficial for patients who are sensitive to preservatives, such as patients with dry eyes, and patients who discontinue medication early as a result of adverse events.

In conclusion, this pharmacodynamic study in patients with glaucoma or ocular hypertension showed that preserved and preservative-free tafluprost achieve equivalent decreases in IOP and both are well tolerated. This study was designed and powered for the pharmacodynamic end-point and, therefore, is limited by the small study population for the safety analysis. Thus, larger-scale studies are required to further investigate the potential benefits of preservative-free tafluprost in the longterm management of patients with glaucoma.

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Conflict of interest

JA, VS and JL have received funding for research carried out in this work by Santen Oy; AR is an employee of Santen Oy; the remaining authors declare no conflict of interests.

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