CLINICAL STUDY REPORT

Version: Final

Report number: 74460 **Total number of pages**: 65 (excluding appendices) **Date**: 11 July 2006

Name of investigational product: Tafluprost (AFP-168) **Phase:** III

Indication: Reduction of intraocular pressure

Title: Efficacy and safety of tafluprost 0.0015% eye drops as adjunctive therapy with timolol 0.5% eye drops. A randomised, placebo-controlled, phase III study in patients with open-angle glaucoma or ocular hypertension.

Sponsor's responsible medical monitor: Auli Ropo, MD, PhD
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Date of first patient included: 11 April 2005 (first patient screened)
9 May 2005 (first patient randomized)
Date of last patient completed (6 weeks): 30 November 2005
(12 weeks): 16 January 2006
(Post-study period): 17 February 2006

GCP Statement: The study described within this report was conducted in accordance with Good Clinical Practices (GCP): Consolidated guideline, CPMP/ICH/135/95, the applicable regulatory requirements and the Declaration of Helsinki.

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SYNOPSIS

Name of sponsor/company: Santen Oy **Name of finished product**: Tafluprost (eye drops) **Name of active ingredient(s)**: Tafluprost (AFP-168)	**Individual study table referring to part of the dossier** Volume: Page: Study no.	***(For national authority use only)***

Title of the study:
Efficacy and safety of tafluprost 0.0015% eye drops as adjunctive therapy with timolol 0.5% eye drops. A randomised, placebo-controlled, phase III study in patients with open-angle glaucoma or ocular hypertension.

Principal Investigators and trial centres:
The study was conducted at 10 centers in 4 countries ([redacted]).
A complete list of principal investigators is provided in Section 6

Publication (reference): Not applicable

Date of first patient enrolled: 11 April 2005 (first screened) 9 May 2005 (first randomized) **Date of last patient completed:** 30 November 2005 (6 weeks) 16 January 2006 (12 weeks) 17 February 2006 (Post-study period)	**Phase of development:** III

Objectives:
The objective of this study was to investigate the efficacy and safety of tafluprost 0.0015% eye drops as adjunctive therapy with timolol 0.5% eye drops in open-angle glaucoma or ocular hypertension patients who are only partially controlled with timolol treatment.
The primary hypothesis for efficacy was to show that the intraocular pressure (IOP) lowering effect of tafluprost 0.0015% eye drops is superior to that of vehicle eye drops, when used adjunctively with timolol 0.5% eye drops, at the end of the 6-week randomised treatment period.

Methodology:
Randomized, double-masked, placebo-controlled, parallel-group, multinational and multicenter phase III study.
Efficacy measurement(s): IOP
Safety assessments: Adverse events, best-corrected visual acuity, conjunctival redness, biomicroscopy, ophthalmoscopy, visual field, iris color/eyelash/lid photographs, and resting blood pressure and heart rate.

Number of subjects:
Approximately 200 patients (100 per treatment group) were planned to be enrolled in the study. A total of 185 patients were randomized (96 in the tafluprost group and 89 in the vehicle group)

Diagnosis and criteria for inclusion:
Prostaglandin naïve patients of any race and either sex aged 18 years or more with primary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma or ocular hypertension. Qualified patients were required to have an IOP of 22-30 mmHg in at least one eye in at least one measurement of the diurnal IOP (8:00, 10:00, 16:00) at the baseline visit, after treatment with timolol 0.5% twice daily during the 4-week open-label run-in period.

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Test product, dose and mode of administration, batch numbers:
Tafluprost 0.0015% (batch no. C000401) eye drops, one drop once daily at 20:10 in the designated eye(s) as adjunctive therapy with 0.5% Oftan® Timolol (see section 9.4.2 for batch no.) twice daily at 8:00 and 20:00 in the designated eye(s)

Reference therapy, dose and mode of administration, batch numbers:
Vehicle (batch no. C000301) eye drops, one drop once daily at 20:10 in the designated eye(s) as adjunctive therapy with 0.5% Oftan® Timolol twice daily at 8:00 and 20:00 in the designated eye(s)

Duration of treatment:
12 weeks: A 6-week randomized treatment period (timolol + tafluprost or timolol + vehicle) followed by a 6-week extension period (vehicle switched to tafluprost).

Criteria for evaluation:
Primary efficacy variable:
Change from baseline in the overall diurnal IOP at 6 weeks

Secondary efficacy variables:
Change from baseline in time-wise IOPs (8:00, 10:00 and 16:00) at 6 weeks, change from baseline in the overall diurnal IOPs and timewise IOPs (8:00, 10:00 and 16:00) at weeks 2 and 4 and proportion of responders at 6 weeks.

Extension period efficacy variables:
Change from baseline in the overall diurnal IOP at 12 weeks, change from baseline in time-wise IOPs (8:00, 10:00 and 16:00) at 12 weeks and proportion of responders at 12 weeks

Safety variables:
Adverse events, best-corrected visual acuity, conjunctival redness, biomicroscopy, ophthalmoscopy, visual field examination, iris color/eyelash/eyelid changes, and resting blood pressure and heart rate

Statistical methods:
A repeated measurements analysis of (co)variance (RM AN(C)OVA) model and descriptive statistics for the primary efficacy variable. The superiority of tafluprost 0.0015% vs. vehicle at 6 weeks was evaluated using a 95% confidence interval obtained from the model. Tafluprost was considered superior to vehicle, if the upper limit of the 95% confidence interval (tafluprost-vehicle) did not exceed 0 mmHg (or the corresponding P-value was less than or equal to 0.05). A repeated measurements analysis of (co)variance model and descriptive statistics for the secondary efficacy variables. Descriptive statistics for safety variables. Statistical tests for these, when feasible.

Results:
Efficacy results
In the randomized treatment period, an IOP lowering effect was seen in both treatment groups. However, the effect was clearly and consistently larger in the tafluprost group, being around 2 mmHg. Thus, the RM ANCOVA results for the primary efficacy variable showed unequivocal superiority in both the ITT Efficacy RM-R dataset and the PP Efficacy RM-R dataset. The upper limits of the 95% confidence intervals were -0.66 mmHg ($p<0.001$, ITT Efficacy RM-R) and -0.72 mmHg ($p<0.001$, PP Efficacy RM-R). The pre-specified sensitivity analysis without the covariate (RM ANOVA) showed similar results. The upper limits of the 95% confidence intervals were -0.69 mmHg ($p<0.001$, ITT Efficacy RM-R) and -0.75 mmHg ($p<0.001$, PP Efficacy RM-R). An additional analysis excluding 8 exceptional vehicle responders showed even stronger superiority.

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Safety results

In the randomized treatment period, 40% of the patients reported any adverse events. There were somewhat more ocular adverse events and somewhat less non-ocular adverse events in the tafluprost group than in the vehicle group. In the extension period, approximately 30% of the patients reported any adverse events. The incidence of both ocular and non-ocular adverse events was comparable between the treatment groups. There was one death (unrelated to the study treatment) and one unrelated non-ocular serious adverse event in the tafluprost group during the study. Three tafluprost patients discontinued the study during the randomized treatment period due to adverse event(s): two patients had related allergic conjunctivitis and one patient had possibly related tinnitus, vertigo, blurred vision and eye pruritus. One patient belonging to the vehicle group (switched to tafluprost) discontinued the study during the extension period due to adverse events. One tafluprost patient died during the post-study period.

In both treatment groups, most of the patients had no or mild conjunctival redness during the study. The deteriorations (at least 1 severity score) were mostly seen from Week 2 onwards in the tafluprost group and from Week 8 onwards in the vehicle group (i.e. 2 weeks after switching to tafluprost). In the vehicle group, no changes in iris color, eyelashes nor lids were seen during the randomized treatment period (Week 6). A few changes occurred during the extension period after switching to tafluprost (Week 12). In the tafluprost group, mild iris pigmentation was seen in about 5% of the eyes at Week 6 and 12. In the vehicle group after switching to tafluprost, over 15% of the eyes had mild eyelash signs at Week 12, which is similar to the eyelash signs seen in the tafluprost group at Week 6. At 12 Weeks, almost 70% of the eyes had increased eyelash signs. In the vehicle group, only 1 eye had mild lid pigmentation at Week 12. In the tafluprost group the corresponding figures were 5 at Week 6 and 11 at Week 12. There were no significant findings (other than obviously related to the disease) in the other ocular safety variables.

No clinically significant findings were seen in the vital signs. At week 6, the mean values for systolic and diastolic blood pressure decreased slightly in the tafluprost group and remained stable in the vehicle group. Heart rate remained stable during the study in both treatment groups.

Conclusions:

In the randomized treatment period, an IOP lowering effect was seen in both treatment groups. However, the effect was clearly and consistently larger in the tafluprost group, being around 2 mmHg. Consequently, the results of both the primary statistical analysis (RM ANCOVA) and the unadjusted sensitivity analysis (RM ANOVA) showed unequivocal superiority. In the extension period, the vehicle patients switched to tafluprost reached the same IOP level as the tafluprost patients. The decrease in IOP in the vehicle group after switch to tafluprost was over 2 mmHg.

Regarding safety, the clinically significant differences in favor of vehicle were seen in conjunctival redness, iris color and eyelash changes, which are typical findings for prostaglandins.

Overall, tafluprost when administered adjunctively with timolol can be regarded as efficacious and safe in the treatment of glaucoma and ocular hypertension.

Date of report:
11 July 2006