CLINICAL STUDY REPORT

Version: Final

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

Indication: Reduction of intraocular pressure

Title: Pharmacodynamics of tafluprost 0.0015% eye drops: a comparison between the preserved and unpreserved formulation in patients with open-angle glaucoma or ocular hypertension.

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Date of first patient included: 14 September 2005 (first patient screened)
08 November 2005 (first patient randomized)
Date of last patient completed: 05 April 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:
Pharmacodynamics of tafluprost 0.0015% eye drops: a comparison between the preserved and unpreserved formulation in patients with open-angle glaucoma or ocular hypertension.

Principal Investigators and trial centres:
[redacted]

Publication (reference): not applicable

Date of first patient enrolled: 14 September 2005 (first screened), 08 November 2005 (first randomized) **Date of last patient completed:** 05 April 2006	**Phase of development:** III

Objectives:
The primary objective of the study was to investigate the pharmacodynamics (as expressed in IOP) of two formulations of tafluprost 0.0015% eyedrops (preserved and unpreserved) in patients with open-angle glaucoma or ocular hypertension.

The primary hypothesis for pharmacodynamics was to show that the IOP lowering effect of preserved tafluprost 0.0015% eye drops was equivalent to that of the unpreserved formulation at the end of the 4-week treatment period.

Methodology:
Randomised, investigator-masked, cross-over and multicenter phase III study.
Pharmacodynamic measurement(s): IOP
Safety assessments: Adverse events, best-corrected visual acuity, biomicroscopy, ophthalmoscopy and visual field.

Number of subjects:
At least 40 patients were planned to be enrolled in the study. A total of 43 patients were randomized and 42 patients completed the study.

Diagnosis and criteria for inclusion:
Patients of any race and either sex aged 18 years or more with primary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma or ocular hypertension, and with a known positive treatment response to prostaglandins. Qualified patients were required to have an IOP of 22-34 mmHg in at least one eye at the first baseline 8:00 measurement, after the required washout period.

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Test products, dose and mode of administration, batch No. :
Tafluprost 0.0015 % unpreserved (batch no. 102844) and tafluprost 0.0015 % preserved (batch no. C000401) eye drops, one drop in the affected eye(s) at 20:00 daily for 4 weeks (preserved or unpreserved eye drops) and 4 weeks (unpreserved or preserved eye drops) in a cross-over fashion.

Duration of treatment:
8 weeks (4 weeks for both formulations). Washout of at least 4 weeks between the treatment periods.

Criteria for evaluation:
Primary pharmacodynamic variable:
Change from baseline in the overall diurnal IOP at 4 weeks

Secondary pharmacodynamic variables:
Change from baseline in time-wise IOPs (8:00, 12:00, 16:00 and 20:00) at 4 weeks and change from baseline in the overall diurnal IOP and time-wise IOPs (8:00, 12:00, 16:00 and 20:00) at 1 week

Safety variables:
Adverse events, best-corrected visual acuity, biomicroscopy, ophthalmoscopy and visual field examination

Statistical methods:
A repeated measurements analysis of (co)variance (RM AN(C)OVA) model and descriptive statistics for the primary pharmacodynamic variable. The equivalence of the two tafluprost formulations at 4 weeks was evaluated using a two-sided 95% confidence interval obtained from the model. Equivalence between the two formulations was shown, if the two-sided 95% confidence interval for the difference (unpreserved-preserved) lay entirely within the equivalence range of (-1.5 mmHg, 1.5 mmHg). A repeated measurements analysis of (co)variance model and descriptive statistics for the secondary pharmacodynamic variables. Descriptive statistics for safety variables. The McNemar test was used for the comparison of the most prevalent adverse event(s).

Results:
Pharmacodynamic results
For both the preserved and unpreserved formulation, a similar and clear (over 5 mmHg) IOP lowering effect was seen already at week 1. The IOP lowering effect was sustained and similar for both formulations at week 4. The 95% confidence intervals from the RM ANCOVA model at 4 weeks were (-0.46, 0.49) for the ITT efficacy dataset and (-0.52, 0.42) for the PP efficacy dataset. These 95% confidence intervals lay entirely within the pre-specified equivalence range of (-1.5 mmHg, 1.5 mmHg). Thus, the RM ANCOVA results for the primary pharmacodynamic variable showed equivalence in both datasets. The pre-specified sensitivity analysis without the covariate (RM ANOVA) showed similar results.

The RM AN(C)OVA results for the secondary pharmacodynamic variables were in line with the results for the primary pharmacodynamic variable, and thus supported the conclusion of equivalence between the two formulations.

Safety results
A total of 11 (25.6%) patients for the unpreserved formulation and 7 (16.7%) patients for the preserved formulation reported adverse events. Out of the 31 adverse events, 27 (87.1%) were ocular and 4 (12.9%) non-ocular. There were slightly more patients with ocular adverse events (26% vs. 14%) for the unpreserved formulation. Conjunctival hyperemia was the most

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common adverse event in this study. However, only 2 patients for the preserved formulation and 6 patients for the unpreserved formulation reported conjunctival hyperemia (p=0.125). There were only 4 non-ocular adverse events (1 for unpreserved and 3 for preserved) and all of them were unrelated to tafluprost. Most of the adverse events were of mild severity and none were severe. There were neither serious adverse events nor withdrawals due to adverse events in this study.

The best-corrected visual acuity remained stable throughout the study for both formulations, and only 2 patients for the unpreserved formulation and 1 patient for the preserved formulation had changes from baseline greater than 0.2 LogMAR scores. In the biomicroscopic examination, most of the findings were seen in lens, conjunctiva, lids and cornea, were already present at baseline, and were of mild severity. In the ophthalmoscopic examination, only few changes in vitreous, retina and optic nerve occurred during the study. In the visual field test, a total of 4 patients had clinically significant changes. There were 3 worsenings that were considered mild by the investigator and 1 improvement of the visual field. In conclusion, no unexpected findings were detected in the ocular safety variables.

Conclusions:
For both the preserved and unpreserved formulation, a similar and clear (over 5 mmHg) IOP lowering effect was seen already at week 1. The IOP lowering effect was sustained and similar for both formulations at week 4. The RM ANCOVA results at 4 weeks (the primary pharmacodynamic variable) showed clearcut equivalence between the formulations in both the ITT efficacy and PP efficacy dataset.

Regarding safety, most of the adverse events were ocular and of mild severity, and none were severe. There were neither serious adverse events nor withdrawals due to adverse events in this study. In essence, no unexpected findings were detected in the ocular safety variables. Both formulations were well tolerated and safe.

Date of report:
20 December 2006