CLINICAL STUDY REPORT **Version:** Final

Report number: 77552 **Total number of pages:** 78 (excluding appendices) **Date:** 31 December 2008

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

Indication: Reduction of intraocular pressure

Title: A phase IIIb study on the changes in ocular signs, symptoms and conjunctival inflammatory markers in patients with ocular hypertension or open-angle glaucoma switched from preserved latanoprost 0.005% eye drops to preservative free tafluprost 0.0015% eye drops.

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Date of first patient included: 09 January 2008 (first patient enrolled)

Date of last patient completed: 23 June 2008 (12-week visit)
11 July 2008 (Post-study visit)

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 Clinical Research	Individual trial table referring to part of the dossier	(For National Authority use only)
Name of finished product: Tafluprost (eye drops)	Volume:	
Name of active ingredients: Tafluprost (AFP-168)	Page:	

Title of trial:
A phase IIIb study on the changes in ocular signs, symptoms and conjunctival inflammatory markers in patients with ocular hypertension or open-angle glaucoma switched from preserved latanoprost 0.005% eye drops to preservative free tafluprost 0.0015% eye drops.

Investigators and trial centers:
The study was conducted at 4 centers in [redacted], 2 centers in [redacted] and 6 centers in [redacted]. A complete list of principal investigators for each country is provided in section 6.

Publication (reference): Not applicable

Date of first patient enrolled: 09 January 2008 **Date of last patient completed:** 23 June 2008 (12-week visit) 11 July 2008 (Post-study visit)	**Phase of development:** IIIb

Objectives:
The objective of this study was to investigate whether changes in ocular signs, symptoms and conjunctival inflammatory markers occur when patients are switched from latanoprost 0.005% eye drops with preservative to tafluprost 0.0015% eye drops without preservative.

Methodology:
Open-label, multinational and multicenter phase IIIb study. The outcome and safety measures were evaluated both at 6 and 12 weeks (primary analysis).
Outcome measures: ocular symptoms upon non-instillation (irritation/burning/stinging, foreign body sensation, tearing, itching, dry eye sensation), ocular signs (fBUT, corneal and conjunctival fluorescein staining, blepharitis, conjunctival redness/hyperemia, Schirmer test) and conjunctival inflammatory markers
Safety assessments: adverse events, best-corrected visual acuity, biomicroscopy, ophthalmoscopy, visual field test, intraocular pressure, drop discomfort (upon instillation) and Quality of Life –questionnaire [redacted]

Number of patients:
Approximately 150 were planned to be enrolled in the study. A total of 158 patients were enrolled.

Diagnosis and main criteria for inclusion:
Patients of any race and either sex aged 18 years or more with ocular hypertension, primary open-angle glaucoma or capsular glaucoma treated with latanoprost 0.005% (Xalatan®) for at least six months before screening. Eligible patients were required to have at least two ocular symptoms OR one ocular symptom and one ocular sign at Screening.

Test product, dose and mode of administration, batch number(s):
Tafluprost 0.0015 % (batch no. 115828) unpreserved formulation, one drop once daily at 20:00 in the affected eye(s).

[redacted]

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Reference therapy, dose and mode of administration, batch number(s):
Not applicable.

Duration of treatment:
12 weeks (followed by a post-study period of 1-3 weeks).

Criteria for evaluation:
Primary outcome measures
- Change from baseline in ocular symptoms upon non-instillation at week 6 and 12 (treated eye(s))
- Change from baseline in ocular signs at week 6 and 12 (worse eye)
- Change from baseline in conjunctival inflammatory markers at week 6 and 12 (worse eye)

Safety variables
Extent of exposure, adverse events, best-corrected visual acuity, biomicroscopy, ophthalmoscopy, visual field test, intraocular pressure, drop discomfort (upon instillation) and Quality of Life –questionnaire ([redacted]).

Statistical methods:
Standard statistical methods for paired data in the analyses of changes from baseline in the primary outcome measures, e.g. McNemar's test for binary data, Wilcoxon signed rank test for ordinal data, and paired t-test for continuous data. Descriptive statistics for safety variables.

Results:
Results for outcome measures
For all ocular symptoms, there was a clear shift towards less severe symptoms after switching from latanoprost to tafluprost without preservative. The favorable changes from baseline for all ocular symptoms were statistically highly significant at both 6 and 12 weeks ($p<0.001$) and in general slightly more prominent at 12 weeks.

For all ocular signs, there was a clear shift towards less severe signs after switching from latanoprost to tafluprost without preservative. The favorable changes from baseline for ocular signs were statistically highly significant at both visits and somewhat more prominent at 12 weeks (for tear secretion, the favorable changes from baseline were statistically significant only at 6 weeks).

There was a clear shift towards fewer patients with abnormal levels of HLA-DR-positive epithelial cells and MUC5AC-expressing goblet cells after switching from latanoprost to tafluprost without preservative. For patients with abnormal values at baseline, the favorable changes from baseline were statistically highly significant and somewhat more prominent at 6 weeks.

Safety results
Approximately a quarter of the patients reported any adverse events. Out of the 74 adverse events, 19 (25.7%) were ocular and 55 (74.3%) non-ocular. Only 3 ocular adverse events (eye pain, eye pruritus and blurred vision) for 2 patients were considered related to tafluprost (as judged by the investigator). Only 2 non-ocular adverse events (dry mouth and dry throat) were considered related to tafluprost. There were no deaths during the study. During the 12-week study period, 4 (2.5%) patients experienced serious adverse events. All 4 events were non-ocular and they were judged not related to tafluprost both by the investigator and the sponsor. During the post-study period, one patient experienced a serious adverse event that was judged not related to tafluprost.

There were no significant findings (other than obviously related to ocular hypertension, primary open-angle glaucoma or capsular glaucoma) in best-corrected visual acuity, biomicroscopy, ophthalmoscopy and visual field

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test, and slightly favorable changes from baseline were seen. A good control of IOP was seen at baseline, and it was maintained after switching from latanoprost to tafluprost. The mean IOP values were though slightly smaller after the switch and the differences from baseline (0.54 mmHg at 2 weeks, 0.41 mmHg at 6 weeks and 0.33 mmHg at 12 weeks) were even statistically significant. Also, the patients suffered clearly less from drop discomfort, and the patients' quality of life clearly improved (according to all 11 questions in the [redacted] questionnaire) after switching from latanoprost to tafluprost without preservative.

Conclusions:
For all ocular symptoms, ocular signs and conjunctival inflammatory markers, clearly favorable changes from baseline were seen, which were mostly statistically highly significant. No unexpected adverse events occurred. There were no significant findings in ocular safety, and slightly favorable changes from baseline were seen. After the switch from latanoprost to tafluprost, the mean IOP values were slightly smaller and the differences from baseline were even statistically significant. After switching from latanoprost to tafluprost without preservative, the changes in drop discomfort and quality of life were favorable and statistically highly significant. Thus, switching patients from latanoprost to preservative-free tafluprost significantly reduced ocular symptoms and signs, and improved the patients' quality of life.

Date of the report:
31 December 2008

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