CLINICAL STUDY REPORT **Version:** Final

Report number: 201051 **Total number of pages:** 77 (without appendices) **Date:** 8 October 2012

Name of investigational product: Tafluprost 0.0015%-Timolol 0.5% preservative free fixed dose combination

Indication: Reduction of intraocular pressure (IOP) **Phase:** III

Title: A phase III, randomized, double-masked 6-month clinical study to compare the efficacy and safety of the preservative free fixed dose combination of tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given concomitantly in patients with open angle glaucoma or ocular hypertension

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Date of first patient included: 8 March 2011 (Screening visit)
29 March 2011 (Baseline visit)

Date of last patient completed: 19 April 2012 (Month 6 visit)
3 May 2012 (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 only)
Name of finished product: tafluprost 0.0015%-timolol 0.5% preservative free fixed dose combination (eye drops)	Volume:	
Name of active ingredients: tafluprost (AFP-168); timolol	Page:	

Title of trial:
A phase III, randomized, double-masked 6-month clinical study to compare the efficacy and safety of the preservative free fixed dose combination of tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given concomitantly in patients with open angle glaucoma or ocular hypertension

Investigators and trial centers:
This study was conducted in 35 centers and 7 countries ([redacted]). The principal investigator for each center is given in Section 6.

Publication (reference): Not applicable

Date of first patient randomized: 29 March 2011 (Baseline visit) **Date of last patient completed:** 19 April 2012 (Month 6 visit) 3 May 2012 (Post study visit)	**Phase of development: III**

Objectives:
The objective of this study was to compare the efficacy and safety of the preservative free fixed dose combination of tafluprost 0.0015% and timolol 0.5% eye drops (FDC) to the concomitant administration of preservative free tafluprost 0.0015% and preservative free timolol 0.5% eye drops (CCA).

The primary aim of the study was to demonstrate that after a 6-month treatment period the FDC administered once daily is non-inferior to the concomitant administration of tafluprost 0.0015% eye drops once daily and timolol 0.5% eye drops twice daily in patients with open-angle glaucoma (OAG) or ocular hypertension (OH).

Methodology:
This was a randomized, double-masked, active-controlled, parallel-group, multinational and multicenter phase III study in patients diagnosed with OH or OAG (i.e. primary open-angle glaucoma [POAG], capsular glaucoma or pigmentary glaucoma). The following efficacy, safety and tolerability assessments were performed:

Efficacy assessments: diurnal IOP measurements were performed at 8:00 (± 1 h), 10:00 (± 1 h) and 16:00 (± 1 h) at Baseline and Weeks 2 and 6, and Months 3 and 6. The three time points were chosen, because they represented the expected peak and trough effects of the FDC, timolol and tafluprost. The primary evaluation of IOP was based on the worse eye (i.e. the eye with a higher IOP at the baseline 8:00 measurement); a secondary evaluation was based on the mean over the eyes.

Safety and tolerability assessments: adverse events (AE), ocular safety assessments (best-corrected visual acuity, central corneal thickness (CCT), biomicroscopy, conjunctival redness, ophthalmoscopy and visual field test), systemic safety measurements (blood pressure and heart rate) and tolerability assessments (drop discomfort).

Number of patients:
The planned number of patients was 380 (190 in each treatment group). A total of 400 patients were randomized and treated: 201 patients received the FDC and 199 patients the CCA.

Diagnosis and main criteria for inclusion:
Patients diagnosed with OH or OAG of any race and either sex aged 18 years or more who had an untreated IOP of ≥23 mmHg at the baseline in one or both eyes and also met all the other inclusion and none of the exclusion criteria were included in the study.

[redacted]

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Test product, dose and mode of administration, batch number(s):
The test product was preservative free fixed dose combination of tafluprost 0.0015% and timolol 0.5% eye drops (FDC); FDC eye drops (batch 130296) administered at 8:10 and vehicle for timolol eye drops (batch 130497) at 8:00 and 20:00 in the affected eye(s).

Reference therapy, dose and mode of administration, batch number(s):
The reference product was preservative free tafluprost 0.0015% and timolol 0.5% and eye drops (CCA); tafluprost eye drops (batch 130295) administered at 8:10 and timolol eye drops (batch 130615) at 8:00 and 20:00 in the affected eye(s)

Duration of treatment:
The duration of the treatment period was 6 months.

Criteria for evaluation:
The following efficacy, safety and tolerability variables were defined:

Primary efficacy variable: Change from baseline in the average diurnal IOP at 6 months.

Secondary efficacy variables: Proportion of responders at 6 months (e.g. change from baseline in IOP of 20% or more by steps of 5%; change from baseline in the average diurnal IOP at 2 and 6 weeks, and 3 months; change from baseline in the time-wise IOPs (at 8:00, 10:00, 16:00) at 2 and 6 weeks, and 3 and 6 months.

Safety and tolerability variables: Extent of exposure, AEs, best-corrected visual acuity, CCT, biomicroscopy, conjunctival redness, ophthalmoscopy, visual field test, blood pressure and heart rate, and drop discomfort (see Section 9.5.1 for schedule of assessments)

Statistical methods:
A repeated measurements analysis of covariance (RM ANCOVA) model was used to analyze the primary efficacy variable. A two-sided 95% confidence interval (CI) for the average difference estimated from the model was used in the evaluation of the non-inferiority hypothesis: non-inferiority was established if the upper limit of the confidence interval (FDC-CCA) was less than or equal to the pre-specified margin of 1.5 mmHg. Both the per protocol (PP) and the intention-to-treat (ITT) dataset were used in the evaluation of the primary hypothesis; however in order to avoid increase in the type II error rate the PP dataset was regarded as the primary one (ICH E9, statistical principles for clinical trials). Last observation carried forward (LOCF) imputation method was applied for the ITT dataset.

All continuous secondary efficacy variables were analyzed according to the same principles as the primary efficacy variable. Sensitivity analyses were carried out using a model without the baseline IOPs as covariate (RM ANOVA). The proportion of responders was analyzed using a Cochran-Mantel-Haenszel (CMH) test. The most prevalent AEs and selected ocular safety and tolerability variables were analyzed with the CMH test as well. Changes in blood pressure and heart rate were evaluated using an analysis of variance (ANOVA) model.

Results:
Efficacy: A substantial and comparable reduction of IOP was seen with the FDC and CCA throughout the study. For both treatments, a steady IOP lowering effect (>30% from baseline) was reached already at 2 weeks and the effect sustained up to 6 months. At 6 months, the estimated overall treatment difference (FDC-CCA) for the PP dataset (primary analysis) was 0.308 mmHg with a 95% CI from -0.194 to 0.810 mmHg. The upper limit of the CI was clearly below the pre-specified margin of 1.5 mmHg; thus providing firm evidence on the non-inferiority between the FDC and the CCA. The analysis using the ITT (LOCF) dataset (secondary analysis) confirmed these results; the treatment difference was 0.315 mmHg with a 95% CI from -0.187 to 0.817 mmHg. The analysis without the baseline IOP as a covariate (sensitivity analysis for PP dataset only) gave similar results; the treatment difference was 0.241 mmHg (95% CI from -0.316 to 0.799 mmHg). Taken together, these three analyses provided unequivocal proof that the FDC is non-inferior to the CCA.

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Furthermore, there were no significant differences in the proportion of responders, and all other secondary efficacy variables (overall changes from baseline at 2 and 6 weeks and 3 months; time-wise changes at 2 and 6 weeks, and 3 and 6 months) supported unanimously the non-inferiority of the two treatments. The treatment effect was also consistent across the prospectively defined subgroups.

Safety:
The distribution and the generally mild severity profile of AEs was highly similar between the treatment groups, but the proportion of patients reporting AEs was slightly higher in the CCA group (44.2% vs. 41.8% in the FDC group). Non-ocular AEs were rare and no deaths occurred during the study. 6 (3.0%) patients in the FDC group and 6 (3.0%) patients in the CCA group experienced serious treatment-emergent adverse events and all of them were non-ocular. In total 11 patients discontinued the study due to adverse events.

Visual acuity scores remained stable during the study and there were no differences between the treatment groups. Central Corneal Thickness slightly declined in both groups, also without major treatment differences. The Biomicroscopy examination showed slight differences between the treatments, as especially in conjunctival redness and in the lids fewer findings showed up in the FDC group. The specific conjunctival redness results confirmed the Biomicroscopy result and in addition, a comparison of prior PG users with PG naïve patients revealed a special benefit of the FDC treatment for PG naïve patients. Ophthalmoscopy data again showed very few new findings and comparable results for both treatment groups. The horizontal and vertical cup to disc ratios showed no changes during the study. Likewise, the visual field exams showed only very little changes.

No clinically significant changes were seen in blood pressure. Heart rate was reduced in the CCA group, in a statistically significant manner.

The drop discomfort evaluation showed decreasing discomfort during the study, by number of reporting patients and also by decreasing severity. No statistically significant differences were seen between the treatment groups.

Conclusions:
A substantial and comparable reduction of IOP was seen with the FDC and CCA throughout the study. The primary efficacy variable and the secondary efficacy variables unanimously evidenced non-inferiority between the two treatments in reduction of IOP.

Overall, the study treatments were well tolerated and safe, and the safety/tolerability profile of the two treatments was highly similar and typical for prostaglandins and timolol.

Date of the report:
8 October 2012