CLINICAL STUDY REPORT **Version:** Final

Report number: 201050 **Total number of pages:** 129 (without appendices) **Date:** 27 Feb 2013

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 as individual monotherapies in patients with open angle glaucoma or ocular hypertension

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Date of first patient included: 28 February 2011 (Screening visit)
11 April 2011 (Baseline visit)

Date of last patient completed: 17 September 2012 (Month 6 visit)
24 September 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:	
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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 as individual monotherapies in patients with open angle glaucoma or ocular hypertension

Investigators and trial centers:
This study was conducted in 60 centers and 10 countries [redacted]).The principal investigator for each center is given in Section 6, and the centers are listed by stratum (TM and PG) in Section 10.1.

Publication (reference): Not applicable

Date of first patient randomized: 11 April 2011 (Baseline visit) **Date of last patient completed:** 17 September 2012 (Month 6 visit) 24 September 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 those of the corresponding individual monotherapies.

The primary aim of the study was to demonstrate that after a 3-month treatment period the FDC administered once daily is superior to both tafluprost 0.0015% eye drops (TAF) administered once daily and timolol 0.5% eye drops (TIM) administered twice daily in patients with open-angle glaucoma (OAG) or ocular hypertension (OH) and insufficiently controlled by prostaglandin alone (PG stratum) or timolol alone (TM stratum).

Methodology:
This was a stratified, 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). For both strata (TM and PG), the primary evaluation of efficacy was done at 3 months, and 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), 16:00 (± 1 h) and 20:00 (± 1 h) at Baseline and Weeks 2 and 6, and Months 3 and 6. The four time points were chosen, because they covered the expected peak and trough effects of the FDC, TIM and TAF. 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 of the two 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 220 for the TM stratum (110 patients for the FDC and TIM) and 380 for the PG stratum (190 patients for the FDC and TAF). A total of 189 patients were randomized and treated in the TM stratum (95 patients with the FDC and 94 with the TIM) and 375 patients in the PG stratum (188 patients with the FDC and 187 with the TAF).

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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 inadequately controlled IOP with their prior timolol (TM stratum) or prostaglandin (PG stratum) monotherapy in one or both eyes and also met all the other inclusion and none of the exclusion criteria were included in the study.

For IOP to be uncontrolled, the patient was to have a clinical need for additional IOP lowering medication as judged by the investigator and at the Screening visit in either treated eye IOP $\geq$ 22 mmHg at any time of the day (TM stratum) or IOP $\geq$ 20 mmHg at any time of the day (PG stratum). Furthermore, at the End-of-run-in visit, after 2-week treatment with preservative-free timolol 0.5% (TM stratum) or preservative-free tafluprost 0.0015% (PG stratum), the patient was to have in either treated eye IOP $\geq$ 22 mmHg at 8:00 (TM stratum) or IOP $\geq$ 20 mmHg at 8:00 (PG stratum). Finally, at the Baseline visit, after a washout period of at least 4 weeks, the patient was to have in either eye an increase of $\geq$ 2 mmHg in the average diurnal IOP (measured at 8:00, 10:00, 16:00 and 20:00) as compared to the average diurnal IOP at the End-of-run-in visit.

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

Reference therapies, doses and modes of administration, batch number:
The reference product in TM stratum was preservative-free timolol 0.5% eye drops (TIM); TIM (batch 130615) was administered at 8:00 and 20:00 in the affected eye(s)

The reference product in the PG stratum was preservative-free tafluprost eye drops (TAF); TAF (batch 130295) was administered at 8:00 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 3 months.

Secondary efficacy variables: Proportion of responders at 3 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 6 months; change from baseline in the time-wise IOPs (at 8:00, 10:00, 16:00, 20:00) 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 the schedule of assessments).

Statistical methods:
A repeated measurements analysis of covariance (RM ANCOVA) model was used to analyze the primary efficacy variable within both strata. A two-sided 95% confidence interval (CI) for the average difference estimated from the model was used in the evaluation of superiority hypothesis: superiority was established if the upper limit of the CI (FDC-TIM in TM stratum; FDC-TAF in PG stratum) was less than 0 mmHg (or, equivalently, the corresponding p-value was less than 0.05). The intention-to-treat (ITT) dataset was used in the analysis of efficacy, but the evaluation of the primary hypothesis was also done using the PP dataset. Last observation carried forward (LOCF) was the primary method of handling missing data for the ITT datasets at 3 months (see also Section 11.4.2.2).

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 diurnal IOP as a covariate (RM

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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 for prior timolol users (TM stratum): A substantial reduction of IOP from baseline was seen with the FDC and TIM throughout the study. For both treatments, a steady IOP lowering effect was reached already at 2 weeks (27.6% for the FDC and 26.2% for the TIM) and the effect sustained up to 6 months. From 6 weeks onwards the decrease was on average 32.0% for the FDC and 28.5% for the TIM. At 3 months, the estimated overall treatment difference (FDC-TIM) for the ITT LOCF dataset (primary analysis) was -0.885 mmHg with a 95% CI from -1.745 to -0.024 mmHg (p=0.044); thus providing evidence on the superiority of the FDC over TIM. The analysis using the PP dataset (secondary analysis) confirmed these results: the treatment difference was -0.968 mmHg with a 95% CI from -1.689 to -0.246 mmHg (p=0.009). The analysis without the baseline IOP as a covariate (sensitivity analysis for the ITT LOCF dataset) gave similar results; the treatment difference was -1.105 mmHg (95% CI from -1.995 to -0.215 mmHg; p=0.015). Taken together, these three analyses provided solid proof that the FDC is superior to the TIM.

Furthermore, there was a clear numerical advantage for the benefit of the FDC in the proportion of responders at 3 months, and the remaining secondary efficacy variables mostly supported the superiority of the FDC (i.e. the overall changes from baseline at 6 weeks and 6 months; the time-wise changes at 6 weeks, and 3 and 6 months). The treatment effect (superiority) was also consistent across the prospectively defined subgroups.

Efficacy for prior prostaglandin users (PG stratum): A substantial reduction of IOP from baseline was seen with the FDC and TAF throughout the study. For both treatments, a steady IOP lowering effect was reached already at 2 weeks (31.8% for the FDC and 26.7% for the TAF) and the effect sustained up to 6 months. From 6 weeks onwards the decrease was on average 32.8% for the FDC and 27.6% for the TAF. At 3 months, the estimated overall treatment difference (FDC-TAF) for the ITT LOCF dataset (primary analysis) was -1.516 mmHg with a 95% CI from -2.044 to -0.988 mmHg (p<0.001); thus providing firm evidence on the superiority of the FDC over TAF. The analysis using the PP dataset (secondary analysis) confirmed these results: the treatment difference was -1.476 mmHg with a 95% CI from -1.965 to -0.987 mmHg (p<0.001). The analysis without the baseline IOP as a covariate (sensitivity analysis for the ITT LOCF dataset) gave similar results; the treatment difference was -1.402 mmHg (95% CI from -1.996 to -0.807 mmHg; p<0.001). Taken together, these three analyses provided unequivocal proof that the FDC is superior to the TAF.

Furthermore, there was a marked numerical and statistical advantage for the benefit of the FDC in the proportion of responders at 3 months, and the remaining secondary efficacy variables supported unanimously the superiority of the FDC (i.e. the overall changes from baseline at 2 and 6 weeks and 3 months; the time-wise changes at 2 and 6 weeks, and 3 and 6 months). The treatment effect (superiority) was also consistent across the prospectively defined subgroups, but somewhat more pronounced in patients with a higher (level of) baseline IOP.

Safety for prior timolol users (TM Stratum): The proportion of patients reporting AEs was slightly higher in the FDC group, compared to the TIM arm (45.3% vs. 37.2%), and while there were more ocular events in the FDC group, there were more non-ocular events in the TIM group. There were no deaths during the study. In total there were 6 SAEs, reported for 2 patients in the FDC group (2.1%) and 4 patients in the TIM group (4.3%). None of these were treatment related and only one was ocular (retinal vein occlusion, TIM).

In the visual acuity examinations, neither differences between the treatment groups nor relevant changes were seen. The difference in Central Corneal Thickness was statistically significant, as it slightly decreased in the FDC group and did not change in the TIM group. Biomicroscopy examinations showed stable results during the study, with slightly more new findings in the FDC group, especially in the conjunctiva. This was confirmed in the conjunctival redness evaluation, where patients in the TIM group showed lower levels of redness and a higher proportion of

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patients with low or no redness. Ophthalmoscopy showed only very few findings overall. The visual field tests showed changes from screening in about 25% of the patients in both treatment arms, with an overall trend for improvement and no differences between the treatment arms.

No clinically significant changes were seen in blood pressure or heart rate.

The drop discomfort levels were generally very low, and even if the descriptive values showed slightly higher levels for the TIM group, the difference was not statistically significant.

Safety for prior prostaglandin users (PG Stratum): The proportion of patients reporting AEs was somewhat higher in the FDC group (44.7%), compared to the TAF arm (38.0%). There were more ocular and non-ocular events in the FDC group, but when looking at related events only, the treatment arms were very similar. There were no deaths during the study. SAEs were reported for 5 patients in the FDC group (2.7%) and 4 patients in the TAF group (2.1%) and all were non-ocular and not related to study treatment.

Visual acuity remained stable over the study period and no differences between the treatment arms were seen. Central Corneal Thickness declined slightly in both FDC and TAF groups: the change was bigger in the FDC group and the difference to TAF was statistically significant (p=0.048). In Biomicroscopy it was shown that the proportion of eyes with abnormal findings stayed constant during the study, with only small differences between the groups. By far the most prevalent new finding was redness, to a comparable extend in both treatment groups. In the conjunctival redness results however, an initial increase early in the study was clearly more profound in the TAF group. In the ophthalmoscopy examination, very few findings were found overall, with comparable results over the treatment arms. Visual field tests showed changes in 18.2% of the patients in the FDC group and 21.8% in the TAF group. In both groups the number of abnormal findings decreased during the 6 Month study period.

No clinically significant changes were seen in blood pressure or heart rate in either group, although in the FDC group the pulse rate decreased slightly.

Assessed drop discomfort levels were very low and also very similar between the treatment arms. No statistically significant difference could be found between the FDC and TAF groups.

Conclusions:
The IOP lowering effect of the preservative-free fixed-dose combination of tafluprost 0.0015% and timolol 0.5% eye drops was substantial, consistent within the two strata and superior to that of tafluprost 0.0015% and timolol 0.5% eye drops given as individual monotherapies in patients with ocular hypertension or open-angle glaucoma.

Overall, the study treatments were safe and well tolerated. The safety profile was well in line with the known side effects of the beta blocker Timolol and the prostaglandin derivate Tafluprost.

Date of the report:
27.2. 2013

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