SYNOPSIS

Name of Sponsor/Company Santen Oy	Individual trial table referring to part of the dossier	(For National Authority use only)
Name of finished product: Tafluprost 0.0015%-timolol 0.5% preservative-free fixed dose combination eye drops (Taptiqom®)	Volume:	
Name of active ingredients: Tafluprost (AFP-168), timolol	Page:	

Title of trial:
A phase IV study on the changes in ocular signs and symptoms in patients with ocular hypertension or open-angle glaucoma switched from Ganfort® eye drops (bimatoprost 0.03%-timolol 0.5%) to Taptiqom® eye drops (tafluprost 0.0015%-timolol 0.5%).

Investigators and trial centers:
The study was conducted at 16 centers in Finland, Germany, Italy and the UK. A complete list of the principal investigators is provided in Section 6.

Publication (reference): Not applicable

Date of first patient enrolled: 23 June 2015 **Date of last patient completed:** 26 April 2016 (12-week visit) 25 May 2016 (Post-study visit)	**Phase of development:** IV

Objectives:
To investigate whether changes in ocular signs or symptoms occur when patients with open-angle glaucoma (OAG) or ocular hypertension (OH) were switched from preservative-free (PF) or benzalkonium chloride (BAK)-preserved Ganfort® eye drops to PF Taptiqom® eye drops.

Methodology:
Open-label, multinational, multicenter, phase IV study. Primary evaluation of outcome measures at 12 weeks.

Outcome measures: ocular symptoms upon non-instillation (irritation/burning/stinging, foreign body sensation, tearing, itching, and dry eye sensation) and ocular signs (fluorescein tear break-up time fBUT, corneal and conjunctival fluorescein staining, blepharitis, conjunctival redness/hyperemia, and tear secretion Schirmer test).

Ocular symptoms and signs were graded and classified as abnormal as follows:

Ocular symptom	Grading	Abnormality criteria
Irritation/burning/stinging	0-4[1]	At least grade 2
Foreign body sensation	0-4[1]	At least grade 2
Tearing	0-4[1]	At least grade 2
Itching	0-4[1]	At least grade 2
Dry eye Sensation	0-4[1]	At least grade 2

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Ocular sign	Grading/Unit	Abnormality criteria
Conjunctival redness/hyperemia	0-4[6]	At least grade 1
Fluorescein tear break-up time (fBUT)	seconds[2]	< 10 seconds
Corneal fluorescein staining	0-V[3]	At least grade I
Conjunctival fluorescein staining	0-X[4]	At least grade II
Blepharitis	0-3[5]	At least grade 1
Tear secretion	mm[7]	≤ 10 mm

[1] 0=None, 1=Trace, 2=Mild, 3=Moderate, 4=Severe
[2] Slit lamp microscope
[3] Oxford grading scale (0-V)
[4] Combined nasal (0-V) and temporal (0-V) score by Oxford grading scale
[5] 0=None, 1=Mild, 2=Moderate, 3=Severe
[6] Redness scale with reference photographs (half-grades allowed):
0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Very Severe
[7] Schirmer test

Safety assessments: adverse events (AEs), best-corrected visual acuity, biomicroscopy, ophthalmoscopy, visual field test, intraocular pressure (IOP), drop discomfort (upon instillation) and Quality of Life –questionnaire (COMTol)

Number of patients:
Approximately 120 patients were planned to be enrolled in the study. A total of 123 patients were enrolled: 76 prior BAK Ganfort® users and 47 prior PF Ganfort® users. The ITT dataset (N=121) excluded two PF Ganfort® users with no post-Screening data. The PP dataset (N=117) excluded all data from additional four patients with major protocol violations.

Diagnosis and main criteria for inclusion:
Patients of any race and either sex aged 18 years or over diagnosed with OH or OAG (primary open angle glaucoma and pseudoexfoliation glaucoma) and treated with PF or BAK-preserved Ganfort® in the evening for at least four weeks before Screening were included. Eligible patients were required to have at least a mild ocular symptom and moderate conjunctival redness/hyperemia at Screening, and at most an IOP of 21 mmHg.

Test product, dose and mode of administration, batch number(s):
Taptiqom®, a PF fixed-dose combination formulation of tafluprost 0.0015% and timolol 0.5%, one drop once daily at 21:00 in the affected eye(s). Bulk batch 30001-A or 30001-A/J, kit labeling batches L15002-7. Expiry date 10/2017.

Reference therapy, dose and mode of administration, batch number(s):
Not applicable. Ganfort®, a PF or BAK-preserved fixed-dose combination of bimatoprost 0.03% and timolol 0.5% dosed once daily in the evening, was to be used by the patients for at least four weeks prior to Screening

Duration of treatment:
12 weeks (followed by a post-study period of 1-3 weeks and medication prescribed by the investigator).

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Criteria for evaluation:

Outcome measures (primary)

- Change from Screening/Baseline in conjunctival redness/hyperemia at 12 weeks
- Change from Screening/Baseline in the worst ocular symptom (irritation/burning/stinging, foreign body sensation, tearing, itching, or dry eye sensation) at 12 weeks

Outcome measures (secondary)

- Change from Screening/Baseline in the remaining ocular signs (fBUT, corneal and conjunctival fluorescein staining, blepharitis, tear secretion Schirmer test) and symptoms (except the worst symptom) at 12 weeks

The changes from Screening/Baseline in ocular signs and symptoms at the remaining visits Week2, Week 6 and post-study were summarized.

Safety and QoL variables

Extent of exposure, AEs, best-corrected visual acuity, biomicroscopic findings, ophthalmoscopic findings, visual field test, IOP, drop discomfort (upon instillation) and COMTol domains and global assessments.

Statistical methods:

Standard statistical methods for paired data were used to analyze the outcome measures (e.g., McNemar's test for binary data, Wilcoxon's signed rank test for ordinal data, and paired t-test for continuous data). A generalized linear mixed model (RM ANCOVA) was used for IOP. Descriptive statistical analyses were applied for the remaining safety variables.

Results:

Outcome results (N=121, ITT dataset)

At Screening, the percentage of patients with abnormal ocular symptoms varied from 40.8% (tearing) to 72.4% (irritation/burning/stinging) for prior BAK Ganfort® and from 42.2% (foreign body sensation) to 71.1% (irritation/burning/stinging) for prior PF Ganfort®. The largest differences between the prior BAK and PF Ganfort® groups were seen in tearing (40.8% vs. 55.6%) and foreign body sensation (53.9% vs. 42.2%). There was a consistent shift towards less severe grades in all ocular symptoms after switching from (BAK-preserved or PF) Ganfort® to (PF) Taptiqom®, and only occasional worsenings occurred during the study. The favorable changes were seen already at 2 weeks and no substantial evidence of heterogeneity was found between the subgroups in the course of the study. The changes were most pronounced at 12 weeks ($p<0.001$, primary evaluation), where the percentage of patients with any improvement ranged from 71.6% (dry eye sensation) to 81.8% (worst ocular symptom). In detail, the 12-week figures were from 71.9% (dry eye sensation) to 84.2% (worst ocular symptom) for prior BAK Ganfort® and from 67.9% (tearing) to 80.8% (foreign body sensation) for prior PF Ganfort®. Concordantly, the number of abnormal symptoms had significantly reduced ($p<0.001$ for all symptoms, McNemar's exact test) and varied from 20.2% (foreign body sensation, tearing) to 41.2% (worst ocular symptom). The proportion of entirely symptom-free patients increased to 18.4% (from zero at Screening).

At Screening, the percentage of patients with abnormal ocular signs varied from 42.1% (blepharitis) to 100.0% (conjunctival redness/hyperemia) for prior BAK Ganfort® and from 48.9% (blepharitis) to 100.0% (conjunctival redness/ hyperemia) for prior PF Ganfort®. Apart from the equal conjunctival redness/hyperemia, higher Screening incidences were seen with PF Ganfort®. The largest difference was in corneal fluorescein staining (82.9% vs. 93.3%). There was a steady shift towards less severe grades in all ocular signs after switching from Ganfort® to Taptiqom®, and only occasional worsenings occurred during the study. The favorable changes were seen already at 2 weeks and no substantial evidence of heterogeneity was found between the subgroups in the course of the study. Overall, the changes were most prominent at 12 weeks ($p<0.001$, primary evaluation), where the percentage of patients with any improvement ranged from 55.2% (corneal fluorescein staining) to 89.3% (conjunctival redness/hyperemia). In detail, the 12-week figures were from 52.4% (corneal fluorescein staining)

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to 90.8% (conjunctival redness/hyperemia) for prior BAK Ganfort® and from 54.5% (blepharitis) to 86.7% (conjunctival redness/hyperemia) for prior PF Ganfort®. Concordantly, the number of abnormal values had significantly reduced (p=0.012 or lower for all signs, McNemar's exact test) and varied from 27.2% (blepharitis) to 76.3% (corneal fluorescein staining).

In summary, no clear advantages of PF Ganfort® over BAK Ganfort® were seen in the Screening incidences of ocular symptoms and signs. All ocular symptoms and signs improved markedly after the switch to Taptiqom®. The greatest improvements were seen with the primary outcome variables.

Safety results (N=123 Safety dataset)

The mean exposure to Taptiqom® was 80 days (N=123). Only one patient experienced a treatment-emergent serious adverse event (SAE) after switching from (prior BAK-preserved) Ganfort® to Taptiqom®: arterial occlusive disease, not related to the study drug. A total of 5 patients (out of 9 patients) discontinued the study due to AE(s).

A total of 76 AEs were reported by 42 (34.1%) patients during the study. Of these, a total of 70 events were reported as treatment-emergent by 41 (33.3%) patients: 15 as ocular events in 12 (9.8%) patients and 55 as non-ocular events in 34 (27.6%) patients. Most of the AEs were either mild (54 events) or moderate (13 events) in severity. Only 3 events (in 2 patients) were severe.

A total of 12 AEs in 10 (8.1%) patients were classified as related to Taptiqom®. Seven of these events were ocular and none of them were unexpected. Exactly one-half of the related AEs were reported in connection with a discontinuation. These related AEs that led to discontinuation were either moderate (5 AEs) or severe (1 AE).

The LogMAR scores remained stable throughout the study in the visual acuity evaluation, and only changes for 7 patients (5.7%) were considered clinically significant (deterioration by 0.2 logMar). Most of the findings in the Screening biomicroscopic evaluation were seen in the lens and lids, and they were of mild severity. Overall, there was a shift towards fewer findings with milder severity during the study, and only sporadic new findings (including worsenings from Screening) were reported. The majority of these new findings were PGA-mediated reversible effects seen in the lids. The frequency and severity of the ophthalmoscopy findings were quite similar at Screening and 12 weeks, and new findings (including worsenings from Screening) were reported in only 7 (5.7%) patients. The results for the visual field test were similar at Screening and post study: only 5 (4.1%) patients had a new finding (including a worsening from Screening) in the test result. It is noteworthy that a variety of IOP-lowering medications were introduced post study beyond the 12-week treatment period with Taptiqom®.

A good control of IOP was seen at Screening, and the control was maintained after switching from Ganfort® to Taptiqom®. The IOP was kept ≤21 mmHg (entry criteria) for almost all patients (>97%), and the 95% CIs for the mean IOP change from Screening at 2, 6, and 12 weeks were all entirely within the ±1 mmHg range of clinical equivalence.

In all, 39% of the patients suffered from moderate to severe drop discomfort at Screening. The incidence and severity of drop discomfort reduced clearly after switching from Ganfort® to Taptiqom® (p<0.001). At 12 weeks, 57% of the patients had less drop discomfort and only sporadic worsenings were seen. Thus, only less than 3% of the patients complained of moderate drop discomfort at 12 weeks (0% severe discomfort).

Favorable changes from Screening were seen in most of the side effect domains (ocular symptoms, taste, vision, accommodation and browache) and activity limitation domains (driving, reading, moderate activities) of the QoL questionnaire COMTol. In essence, the global assessment results (treatment preference, effect of side effects/ activity limitations on QoL, compliance and treatment satisfaction) strengthened the earlier outcome results and

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affirmed the good correlation between improved ocular tolerability and QoL.

In summary, no unexpected related AEs occurred after switching from Ganfort® to Taptiqom®. Neither were there any significant findings in ocular safety; in contrast, some favourable changes from Screening were seen. A good control of IOP was maintained. The changes in drop discomfort and QoL were also clearly in favor for Taptiqom®.

Conclusions:
PF Taptiqom® eye drops offered clinical benefits to OH/OAG patients that outweighed those of the PF/BAK-preserved Ganfort® eye drops. IOP remained controlled and PF Taptiqom® significantly decreased the signs and symptoms of ocular surface disease. PF Taptiqom® also outrated PF/BAK-preserved Ganfort® in drop comfort, QoL, treatment satisfaction and treatment preference.

Date of the report:
31 January 2017