CLINICAL STUDY REPORT

[redacted]

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Name of investigational product: NA

Observational study

Indication: Ocular hypertension, Glaucoma

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Title: **Cross-sectional study to investigate the occurrence and severity of signs and symptoms of ocular surface disease in patients with ongoing chronic topical treatment for glaucoma or ocular hypertension**

Sponsor's responsible medical monitor:
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Date of first patient included: 14.2.2011
Date of last patient last visit: 29.12.2011
Date of last patient telephone interview: 10.01.2012

GCP Statement: The study described within this report was conducted in accordance with Good Clinical Practices (GCP): Consolidated guideline, CPMP/ICH/135/95.

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SYNOPSIS

Name of sponsor/company: Santen Oy **Name of finished product**: **Name of active ingredient(s)**:	**Individual study table referring to part of the dossier** Volume: Page: Study no.	***(For national authority use only)***

Title of the study:
Cross-sectional study to investigate the occurrence and severity of signs and symptoms of ocular surface disease in patients with ongoing chronic topical treatment for glaucoma or ocular hypertension

Principal Investigators and trial centres:
[redacted]
13 active Investigators in [redacted]

Publication (reference):

Date of first patient included: 14.2.2011 **Date of last patient last visit:** 29.12.2011 **Date of last patient telephone interview:** 10.01.2012	**Clinical Phase:** Observational study (Phase IV)

Objectives:
To investigate the occurrence and severity of signs and symptoms of ocular surface disease (OSD) in patients with ongoing chronic topical treatment for glaucoma or ocular hypertension, and to correlate the findings to the exposure of the eye to benzalconium chloride (BAC) in the eye drops used.

Methodology:
Signs: ophthalmologic examination of the eyelids with severity grading of findings, evaluation of conjunctival hyperemia using reference photographs, examination of corneal and conjunctival surface using fluorescein staining (Oxford grading), fluorescein tear fluid break up time (fBUT), Schirmer's test and measurement of IOP.
Symptoms: separate telephone contact by an independent nurse to assess subjective symptoms of irritation/burning/stinging, itching, foreign body sensation, tearing, and dry eye sensation.

Number of subjects:
The plan was to enroll approximately 800 patients and 80 control patients. Eventually, 51 control patients and 568 patients were enrolled. Evaluation of ocular signs was based on the information received from 1053 treated eyes of 564 patients. Evaluation of ocular symptoms was given by 562 patients.

Diagnosis and criteria for inclusion:
The study patients had a diagnosis of ocular hypertension (OH) or glaucoma (primary open angle glaucoma [POAG], pseudoexfoliation glaucoma [PEX], pigmentary glaucoma) in either eye or both eyes, for which they had current treatment. Study patients had to be at least 18 years of age; the limit for control patients was at least 40 years.

Test product, dose and mode of administration, batch No. : NA

Duration of treatment: NA

Reference therapy, dose and mode of administration, batch No.: NA

Criteria for evaluation:

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Occurrence and severity of ocular signs and symptoms
Comparison of variables between case patient and control patient groups
Relationship between number of BAC drops in daily treatment of the case patients and ocular signs and symptoms
Relationship between number of active compounds in daily treatment of the case patients and ocular signs and symptoms
Concordance between findings made by ophthalmologist and symptoms reported to a nurse by the patients

Statistical methods:
No formal statistical hypothesis was set. Statistics was largely descriptive and illustrated with graphical methods for data analysis. Statistical comparison between case and control patient groups and relationships between the type of treatment and exposure of the eye to BAC (preservative) was analyzed using generalized linear nodels with appropriate distribution and link functions. the concordance was investigated using an appropriate coefficient for agreement.

Results:

Most common glaucoma therapy classes of the case patients were monotherapy with prostaglandins (384 treated eyes = 36.5%), beta blocker & prostaglandin fixed-dose combination (293 treated eyes = 27.8%) and prostaglandins with concomitant beta blocker & other fixed-dose combination (109 treated eyes = 10.3%).

Ocular signs:
A clear difference between case and control patients was seen for all variables except Schirmer's test. Mean values of ocular signs between case and control patients were: eyelid redness 0.92 vs 0.04 ($p<0.001$), conjunctival redness 1.92 vs 1.18 ($p<0.001$), corneal fluorescein staining 1.3 vs 0.8 ($p=0.006$), combined conjunctival fluorescein staining 2.8 vs 2.0 ($p=0.0054$), fBUT 5.2 s vs 7.3 s ($p=0.0083$) and Schirmer's test 10.8 mm vs 11.9 mm ($p=0.36$).
When looking at number of abnormal ocular signs per patient, it was also clear that OSD signs were more common within the case patient group: 93% had two or more abnormal ocular signs and in 16% all six signs studied were abnormal. Sixteen percent (16%) of the control patients had no abnormal signs whereas only 1% of the case patients were free of OSD signs. This difference in the prevalence between the case and control patients was statistically significant ($p<0.001$).

With the exception of Schirmer's test, the severity of ocular signs was shown to worsen by the number of active compounds as well as by number of BAC containing drops in daily treatment of the case patients. The risk for most severe ocular signs was the highest in patients with four or more active compounds or BAC drops daily.
The same finding was made for the overall signs score, which was calculated as a summary of the individual signs in each eye. The mean overall signs score declined by increase in number of active compounds and BAC drops ($p<0.001$ for both).

Mean IOP levels were the same between the treated case patients and untreated control patients (17-18 mmHg).

Ocular symptoms:
No significant differences were observed between the symptoms (irritation/burning/stinging, itching, foreign body sensation, tearing, and dry eye sensation) reported by the case and control patients. Biggest difference was seen in dry eye sensation ($p=0.04$); about 60% of the case patients compared to 76% of the control patients reported no dry eye sensation. Depending on the individual symptom, about 60-80% of the case patients reported not having any bother of this symptom. Clear statistically significant correlation between most of the individual symptoms, or the sum of symptoms score, and number of active compounds or BAC drops could not be shown. Only in dry eye sensation, the severity of the symptom worsened by increase in number of active compounds ($p<0.01$). Also in foreign boy sensation, the risk for more severe symptom seemed to worsen by increase in number of active compounds and BAC drops ($p<0.05$).

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Ocular signs vs symptoms:
The overall signs score was at its highest at 0.11 (indicating presence of fewer/milder signs) in the lowest category 0 of the sum of symptoms score. Thereafter the overall signs score declined down to -0.38 in the highest category 10+ of the sum of symptoms score (p for linearity <0.001). Thus, OSD signs objectively noted by ophthalmologists may be in concordance with the symptoms subjectively perceived by the patients.

SUMMARY - CONCLUSIONS

In the outpatient population studied, the objective signs of OSD were common in patients treated with IOP-lowering topical ocular medications; 93% of them had at least two abnormal ocular signs and in 16 % of the patients all investigated signs were abnormal.

With the exception of Schirmer's test, the severity of ocular signs was shown to worsen by the number of active compounds as well as by number of BAC containing drops in daily treatment of the patients. The risk for most severe ocular signs was the highest in patients with four or more active compounds or BAC drops in daily treatment.

The subjective ocular symptoms were, on the other hand, more uncommon; depending on the individual symptom, about 60-80% of the case patients reported *not* having any bother of this symptom.

Date of report: February 2015

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