CLINICAL STUDY REPORT

Version: Final

Report number: 73652 **Total number of pages**: 35 (excluding appendices)

Date: March 12, 2008

Name of investigational product: Timosan® and Oftan Timolol® **Phase: IV**

Indication: Timolol concentration in the aqueous humor

Title: Corneal penetration of timolol into the human aqueous humor after administration of 0.1% timosan eye gel or 0.5% timolol eye drops

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Sponsor's responsible medical monitor:
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Manager, Medical Affairs
Santen Oy

Date of first subject included: May 16, 2006
Date of last subject completed: November 28, 2006

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

Sponsor

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SYNOPSIS

Name of sponsor/company: Santen Oy **Name of finished product:** Timosan® **Name of active ingredient(s):** timolol	**Individual study table referring to part of the dossier** Volume: Page: Study no.	***(For national authority use only)***
Title of the study: Corneal penetration of timolol into the human aqueous humor after administration of 0.1% timosan eye gel or 0.5% timolol eye drops		
Principal Investigators and trial centres: [redacted]		
Publication (reference): -		
Studied period: Six months first enrollment May 16, 2006 last completed November 28, 2006	**Clinical Phase:** IV	
Objectives: The primary objective of the study was to compare concentration of timolol in the human aqueous humor after single administration of timolol 0.1% eye gel (Timosan@) or aqueous timolol 0.5% eye drops (Oftan Timolol@) in patients scheduled for cataract surgery. The secondary objectives: - To analyze timolol metabolites in aqueous humor in order to find out indirect evidence of CYP2D6 mediated metabolism in ocular tissues. - To measure the thickness of cornea and tear production (Schirmer's test) and to relate them to the penetration of timolol into the human aqueous humor.		
Methodology: A phase IV, randomised, investigator masked study.		
Number of subjects: (planned/analyzed) 44/43 (44 patients were randomized. All patients completed the study. However, the aqueous humor sample of one patient was contaminated. Therefore the total number of patients in the analyses was 43.)		
Diagnosis and criteria for inclusion: Patients of any race and either sex meeting all of the following criteria were considered eligible for this study. The patients had to 1. be 55-80 years 2. be in good general health 3. be scheduled for cataract surgery 4. provide a written informed consent		
Test product, dose and mode of administration, batch No. : Timolol 0.1% eye gel (Timosan@), one drop once on the eye to be scheduled for cataract operation		
Duration of treatment: Single administration		
Reference therapy, dose and mode of administration, batch No.: Timolol 0.5% eye drops (Oftan Timolol@), one drop once on the eye scheduled for cataract operation.		

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Criteria for evaluation:
Efficacy
Timolol concentration in aqueous humor was measured. Efficacy was evaluated indirectly by calculating the β-receptor occupancy. Measured timolol concentration in aqueous humor was used in calculations.

Safety
Adverse events were recorded.

Statistical methods: The statistical significance between the groups was evaluated by permutation type test. However, as sample size was small and variables were skewed, resampling-based (bias-corrected bootstrap, 1000 replications) method was used to derive 95 per cent confidence intervals. Correlation coefficient were analysed by using Spearman method.

SUMMARY - CONCLUSIONS

Efficacy results
The mean timolol concentration in the aqueous humor was 210 ng/ml (SD 175 ng/ml) after administration of Timosan@ and 538 ng/ml (SD 304 ng/ml) after administration of Oftan Timolol@. Variability in timolol concentration is more stable after administration of timolol eye gel as compared with aqueous timolol eye drops.

β_1-receptor were 99.8% and 99.9% occupied with mean timolol concentrations in aqueous humor after administration of Timosan® and Oftan Timolol®, respectively. β_2-receptors were 99.9% and 100% occupied with mean timolol concentrations after administration of Timosan@ and Oftan Timolol@, respectively.

The lowest timolol concentration in aqueous humor was 76 ng/ml in a patient in Timosan@ group. With this timolol concentration β_1-receptor occupancy was 99.5 % and β_2-receptor occupancy 99.8 %.

Safety results
There were no adverse events reported after administration of products.

Conclusion
Timolol concentrations detected in aqueous humor after administration of Timosan@ and Oftan Timolol@ suggest that timolol occupies at least 99% of both β1- and β2 -receptors. Timolol aqueous humor concentrations remained lower after use of Timosan®. Since glaucoma drugs may be used for decades, it is important to note that the absorbed drug level in aqueous humor should be as low as possible to avoid toxic consequences. Timolol aqueous humor concentrations remained lower and more stable after the use of Timosan@ as compared with Oftan Timolol@. These findings give further support for excellent risk/benefit ratio of Timosan@.

Date of report:
March 12, 2008

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