Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis is supplied for informational purposes only in the interests of scientific disclosure. It must not be used for any commercial purposes and must not be distributed, published, modified, reused, posted in any way, or used for any other purpose without the express written permission of Boehringer Ingelheim.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alna®, Flomax®				
Name of active ingredient: Tamsulosin hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 19 October 2006	**Number:** U06-1948	**Study period (dates):** 15 NOV 05 to 22 FEB 06		

Title of study:	A parallel group study with three different α-antagonists and placebo once daily over three weeks to assess their influence on the extent of weekly phenylephrine-induced mydriasis at three different concentrations of phenylephrine in healthy male volunteers
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Ingelheim, Boehringer Ingelheim Pharma GmbH & Co. KG,
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The study was aimed to evaluate the pharmacological effect of different α-antagonists on phenylephrine induced pupil size in healthy male volunteers as pharmacological basis for IFIS.
Methodology:	Open-label (persons involved in pupillometry were completely blinded to treatment), randomised, four parallel groups study, static pupillometry before and after mydriasis induction with three different concentrations of phenylephrine (PE) (0.25%, 0.75%, and 2.5%) and three brightness levels (scotopic, mesopic low, and mesopic high) in each subject before as well as after one, two, and three weeks treatment with the same α-antagonist, and one week after last application
No. of subjects:	
planned:	entered: 96
actual:	enrolled: 110 total entered: 97 Tamsulosin 0.4 mg modified release capsules (Alna®): entered: 24 treated: 23 analysed (for primary endpoint): 22 Alfuzosin 10 mg extended release tablets (Uroxatral® uno): entered: 25 treated: 25 analysed (for primary endpoint): 25 Doxazosin 4 mg extended release tablets (Cardular PP Uro®): entered: 24 treated: 24 analysed (for primary endpoint): 24 Placebo: entered: 24 treated: 23 analysed (for primary endpoint): 23

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alna®, Flomax®		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tamsulosin hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 19 October 2006	**Number:** U06-1948	**Study period (dates):** 15 NOV 05 to 22 FEB 06		

Diagnosis and main criteria for inclusion:	Healthy, male, Caucasian, 21 to 55 years old, BMI: 18.5 to 29.9 kg/m^2, signed written informed consent
Test products:	Tamsulosin 0.4 mg modified release capsules (Alna®) Alfuzosin 10 mg extended release tablets (Uroxatral® uno) Doxazosin 4 mg extended release tablet (Cardular PP Uro®)
dose:	Tamsulosin: 0.4 mg qd Alfuzosin: 10 mg qd Doxazosin: 4 mg qd
mode of admin.:	oral
batch no.:	Tamsulosin: B051000602 Alfuzosin: B051001021 Doxazosin: B051000737
Duration of treatment:	22 days
Reference therapy:	Placebo not matching to any of the active treatments
dose:	Not applicable
mode of admin.:	oral
batch no.:	B051000449
Criteria for evaluation:	
Efficacy/Clinical Pharmacology:	Pupillometry (primary parameter)
Safety:	Medical examination, blood pressure, pulse rate, laboratory parameters, adverse events, and assessment of global tolerability
Statistical methods:	Descriptive statistics; analysis of covariance (ANCOVA) for pupillometry endpoints followed by pairwise t-tests of α-antagonists versus placebo, 95% confidence intervals; tabulation of incidence, severity and causal relationship of adverse events (AEs)

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alna®, Flomax®		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tamsulosin hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 19 October 2006	**Number:** U06-1948	**Study period (dates):** 15 NOV 05 to 22 FEB 06		

SUMMARY – CONCLUSIONS:

Efficacy results: *Pupillometry*

The treatment groups were well balanced with respect to demographic and pre-treatment characteristics. The mean pupil diameter calculated under the nine different test conditions (three PE concentrations and three levels of light brightness) was 5.08 ± 0.78 mm before PE administration and 7.12 ± 0.89 mm after PE administration at baseline; thus, administration of PE administration lead to an average pupil dilation of 2.04 mm. Pupil diameters after PE administration were highest in the tamsulosin group (7.35 ± 0.67 mm) and lowest in the group allocated to doxazosin (6.93 ± 0.90 mm). Intrinsic high inter-individual variability of pupil diameter was seen before and after PE administration.

The primary statistical analysis showed a slightly reduced PE induced mydriasis on treatment with tamsulosin compared to placebo, which was statistically significant ($p = 0.0049$). Alfuzosin and doxazosin did not prove different to placebo in the primary endpoint. The placebo-adjusted mean change from baseline in the mean pupil diameter measured over the nine combinations of the three PE concentrations and the three brightness levels was -0.29 mm for tamsulosin ($p = 0.0049$), -0.01 mm for alfuzosin ($p = 0.9387$), and 0.01 mm for doxazosin ($p = 0.9295$).

A slight increase or reduction of mydriasis occurred in all four treatment groups. Maximal reduction of mydriasis compared to baseline was not dependent on the treatment with a specific α_1-antagonist. The maximal decrease from baseline in pupil diameter on treatment was -0.46 mm for placebo, -0.68 mm for tamsulosin, -0.65 mm for alfuzosin, and -0.58 mm for doxazosin and thus only differed slightly between treatments.

The secondary analyses investigating all the different brightness levels and PE concentrations separately revealed that the mean pupil diameter observed in the group treated with tamsulosin was slightly lower on treatment compared to baseline while the mean pupil diameters on treatment with placebo as well as with alfuzosin and doxazosin were slightly higher compared to baseline.

There was no consistent tendency among the treatment groups with regards to reversibility of an effect when comparing the mean change from baseline on day 22 and 29 on treatment with placebo, tamsulosin, alfuzosin, or doxazosin. For placebo and tamsulosin, the magnitude of the change from baseline was similar on day 22 and day 29, whereas the change from baseline decreased for alfuzosin and increased for doxazosin.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alna®, Flomax®		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tamsulosin hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 19 October 2006	**Number:** U06-1948	**Study period (dates):** 15 NOV 05 to 22 FEB 06		

Considering the high inter-individual variability, and the impact of baseline pupil diameter, PE concentration, and light conditions, the effect observed on treatment with tamsulosin was considered small. The reduction of the pupil diameter on treatment with tamsulosin amounted to only about 4% of the mean pupil diameter after PE administration.

Pharmacokinetics

In the pharmacokinetic evaluation, C_{pre} stands for the plasma concentration of each α_1-antagonist about 6 h before PE application (i.e. within 1 h before each α_1-antagonist administration). $C_{PEapplication}$ stands for the plasma concentration of each α_1-antagonist at 1.5 h after PE application (i.e. 6.5 h after each α_1-antagonist administration), which was considered the plasma concentration relevant for the pupillometry measurements on treatment. Pharmacokinetics were assessed at visit 5 to 9.

All the plasma concentrations before α_1-antagonist administration at visit 5 were below the limit of quantification, as expected.

On treatment (visit 6 to 8), the mean values of C_{pre} for tamsulosin HCl ranged from 4.64 to 4.90 ng/mL; the mean values of $C_{PEapplication}$ for tamsulosin HCl varied between 8.97 and 11.0 ng/mL. The mean values of C_{pre} and $C_{PEapplication}$ for alfuzosin were between 2.35 and 3.03 ng/mL and between 5.77 and 7.93 ng/mL, respectively. Mean C_{pre} for doxazosin were 8.43 ng/mL to 9.53 ng/mL; mean $C_{PEapplication}$ were between 11.9 ng/mL and 12.8 ng/mL. Thus, for none of the α_1-antagonists, the values of mean C_{pre} as well as of mean $C_{PEapplication}$ relevantly differed between visits indicating that the plasma concentration of each α_1-antagonist had reached steady state. When analysing the data separately for the different PE concentrations, it was found that, for each of the three α_1-antagonists, the mean values of C_{pre} and $C_{PEapplication}$ were similar between the different PE concentrations. Thus, for each α_1-antagonist, the exposure was comparable at each pupillometry at the three different PE concentrations applied in a three-way cross-over.

At visit 9 after the 7 days washout period, plasma concentrations for tamsulosin, alfuzosin, and doxazosin were below the limit of quantification or had declined to a very low level.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alna®, Flomax®		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tamsulosin hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 19 October 2006	**Number:** U06-1948	**Study period (dates):** 15 NOV 05 to 22 FEB 06		

Safety results:

None of the subjects experienced a serious adverse event (SAE); no 'other significant' adverse event defined as a non-serious AE leading to discontinuation of drug administration or dose reduction occurred during this trial. However, two subjects discontinued the trial due to an AE: one subject was withdrawn because of a sinusitis before the subject received trial medication; one subject experiencing a gastroenteritis stopped trial participation after visit 8 on study day 22 after he had received all doses of α_1-antagonist. Overall, 116 AEs were observed in 61 of the 97 subjects. The majority of AEs observed during the study were of mild intensity; no severe AEs occurred. It was differentiated between AEs occurring on treatment with α_1-antagonist or placebo alone, after the administration of eye drops at baseline and on treatment, and after the administration of eye drops on trial day 29 after cessation of treatment, as well as during screening, during wash-out, post-treatment (with α_1-antagonist or placebo) and post-study.

On treatment with α_1-antagonist or placebo alone, infections and infestations (15 subjects, 15.8%), gastrointestinal disorders (8 subjects, 8.4%), and nervous system disorders (5 subjects, 5.3%) were the AEs with the highest incidence. AEs observed in at least 3 subjects by MedDRA preferred term included rhinitis (6 subjects, 6.3%), nasopharyngitis (5 subjects, 5.3%), headache (5 subjects, 5.3%), fatigue (4 subjects, 4.2%), diarrhoea (3 subjects, 3.2%) and micturition urgency (3 subjects, 3.2%). A total of 16 subjects (16.8%) experienced AEs considered drug-related during the treatment period with α_1-antagonist or placebo alone. When comparing the different α_1-antagonists, the incidence of drug-related AEs was highest in the doxazosin group and lowest in the tamsulosin group (tamsulosin: 4 subjects, 17.4%; alfuzosin: 5 subjects, 20.0%; doxazosin: 7 subjects, 29.2%). In the tamsulosin group, the drug-related AEs included retrograde ejaculation (1 subject), headache (1 subject) , vomiting (1 subject), vertigo (1 subject), dry throat (1 subject), and erythema of eyelid (1 subject). Some of these drug-related AEs were considered drug-related because the investigator saw a reasonable relationship to the application of eye drops.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alna®, Flomax®		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tamsulosin hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 19 October 2006	**Number:** U06-1948	**Study period (dates):** 15 NOV 05 to 22 FEB 06		

A total of 12 subjects (12.6%) were affected by an AE following the administration of eye drops (at baseline: 6 subjects, 6.2%; on treatment with α_1-antagonist or placebo: 6 subjects, 6.2%). The most frequently observed AE was headache; the event was dose-dependent with 1 case occurring at a PE concentration of 0.25%, 4 cases at a PE concentration of 0.75%, and 6 cases at a PE concentration of 2.5%. Headache is a known side effect of PE. Eye disorders were reported in 3 subjects occurring on treatment with the two higher doses of PE (accommodation disorder: 1 subject; eye pruritus: 1 subject; ocular hyperaemia: 1 subject). Headache, visual accommodation disorder, and ocular hyperaemia were considered drug-related by the investigator.

No AEs occurred following administration of PE on day 29.

Four subjects (4.1%) experienced an AE during screening. An AE during the washout period was observed in 27 subjects (27.8%); they were mostly infections and headache. In 6 subjects (6.3%), an AE was observed post-treatment. There was no AE with an onset after the end-of-study examination (post-study).

All the subjects affected by an AE fully recovered. The adverse event profile observed in this study was consistent with the results of previous trials in healthy volunteers and with the safety information available on the three α_1- antagonists, PE, and the locally applied anaesthetic proxymetacaine.

The observed changes in laboratory parameters reflect the fluctuations commonly seen in study populations comprising healthy volunteers. Physical examinations, vital signs, and ECGs, and the measurement of intraocular pressure did not show the presence of any abnormalities. The study medications were well tolerated in the majority of subjects.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alna®, Flomax®		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tamsulosin hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 19 October 2006	**Number:** U06-1948	**Study period (dates):** 15 NOV 05 to 22 FEB 06		

Conclusions:

The primary analysis showed a statistically significantly reduced PE induced mydriasis on treatment with tamsulosin compared to placebo while alfuzosin and doxazosin did not prove different to placebo. However, considering the observed high inter-individual variability in pupil diameter, the placebo-adjusted mean in PE induced mydriasis observed on treatment with tamsulosin was small and considered clinically irrelevant. The reduction on treatment with tamsulosin amounted to only about 4% of the mean pupil diameter after PE administration. The light brightness, the PE concentration, and the individual baseline value constituted the main factors determining the pupil diameter. Further studies in patients undergoing cataract surgery would be required to elucidate the underlying mechanisms of IFIS and to investigate whether the PE induced pupil size on treatment with α_1-antagonist is a valid pharmacological model for IFIS.

The pharmacokinetic data indicated that the exposures were at steady-state levels and were appropriately controlled for the purpose of this study.

The study medications were safe; they were well tolerated in the majority of the subjects.