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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim Pharma KG		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product:				
Name of active ingredient: ESR 1150 CL		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page: to**		**Addendum No.:**
Report date: 11 September 2000	**Number:** 1172.2	**Study period (years):** 7 Feb. - 25 March 2000		

Title of study:	Administration of ESR 1150 CL in ascending doses of 0.5, 1, 2, 4 and 8 mg in an open, group comparison and placebo-controlled design (placebo randomised double blind in the dose groups) for the assessment of safety, tolerability (maximal tolerated dose, MTD), pharmacokinetics and pharmacodynamics in 5 groups of 8 female and 5 male healthy subjects, and 4 mg additionally in fed state, in a cross over design (first part of study). Safety, tolerability and pharmacokinetics of MTD/4, MTD/2 and MTD in 6 healthy male subjects, identified as CYP2D6 and/or "spartein" poor metabolizers, in a 3-fold cross over, open study (second part of study).
Investigator:	[redacted]
Study center(s):	[redacted] Germany
Publication (reference):	not applicable
Clinical phase:	I
Objectives:	safety and tolerability, pharmacokinetics and pharmacodynamics
Methodology:	single ascending dose randomised, open, placebo-controlled (placebo double blind in each dose); cross over for fed state; cross over and open for second part of study
No. of subjects entered:	39 (15 males and 24 females)
total:	39
Diagnosis and main criteria for inclusion:	healthy male and female subjects
Test product:	ESR 1150 CL
dose:	0.5, 1.0, 2.0 mg
mode of admin.:	p.o.
batch no.:	Product 1 (0.5 mg tablet) B99020 BI Japan Product 3 (2.0 mg tablet) B99021 BI Japan
Duration of treatment:	1 single dose

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Reference therapy:	matching placebo
dose:	n.a.
mode of admin.:	p.o.
batch no.:	Product 2 (matching placebo to 0.5 mg tablet) B99022 BI Japan Product 4 (matching placebo to 2.0 mg tablet) B99023 BI Japan
Criteria for evaluation:	
Efficacy:	Pharmacodynamics (free-flow uroflowmetry, radioreceptor assay) and pharmacokinetics of ESR 1150 CL were assessed as surrogate for efficacy data.
Safety:	Adverse events, laboratory, vital sign parameters (PR, BP), ECG, postdose physical examination, global tolerability
Statistical methods:	Linear regression of pharmacokinetic parameters ln(AUC) and ln(C_{max}) versus the logarithmically transformed dose, descriptive statistics for other pharmacokinetic parameters, safety and pharmacodynamic data

SUMMARY - CONCLUSIONS:

Safety results:

Under placebo, there were no adverse events. The frequency of adverse events increased with dose: Under the lowest dose (0.5 mg ESR 1150 CL), 3 subjects reported in total 5 adverse events, under the medium dose (1.0 mg ESR 1150 CL), 5 subjects reported in total 10 adverse events, whereas under the highest dose (2.0 mg ESR 1150 CL), 8 subjects reported in total 23 adverse events.

The adverse events predominantly were gastro-intestinal system disorders, mainly nausea and vomiting. Additionally, central nervous system disorders were reported under all three ESR 1150 CL treatments, e.g. dizziness and headache.

There was a gender difference in adverse event experience: Female subjects were affected more often by adverse events. Male subjects reported adverse events only under 2.0 mg ESR 1150 CL, whereas female subjects experienced adverse events under all 3 doses of ESR 1150 CL. During the whole study, only female subjects vomited.The majority of adverse events were of mild intensity. All events after active treatment were considered to be drug-related. There were no serious adverse events in the study.

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	In view of the increase of adverse event frequency with dose, dose escalation was stopped after 2.0 mg ESR 1150 CL. The planned doses of 4.0 mg and 8.0 mg were not applied during the study. The study arm in poor metabolizers (second part of study) was not performed.
Pharmacodynamic and pharmacokinetic results:	In the free-flow uroflowmetry, mean residual volume was increased 2, 4 and 8 hours after dosing 0.5 mg ESR 1150 CL only. For all the other doses, there was a decrease 2 hours after dosing, followed by an increase towards values, which were comparable to predose values. Mean maximum flow rate was very similar for all treatments. There was a small increase 2 and 4 hours after dosing. Only in the dose group of 1.0 mg, mean maximum flow was clearly lower than baseline 8 hours after dosing. Mean average flow rate showed a very similar pattern for all three doses and placebo: an increase towards 4 hours after dosing, followed by a decrease eight hours after dosing. Mean voiding time was more variable between treatments. Voiding time remained stable for 0.5 mg ESR 1150 CL, but showed a small decrease 8 hours after dosing for placebo, 1.0 and 2.0 mg ESR 1150 CL, which can be explained by the decrease in voiding volume. Mean time to maximum flow mainly was very similar between treatments. As to pharmacokinetics, ESR 1150 was rapidly absorbed at all dose levels. The concentration of the metabolite (CDBG 163) exceeded the concentration of ESR 1150. It was not possible to evaluate whether differences in the pharmacokinetic parameters and cumulative urinary excretions of ESR 1150 and CDBG 163 among the three dose groups and between male and female were significant because of high inter-subject variability.
Conclusions:	In view of the increase of adverse event frequency with dose, dose escalation was stopped after 2.0 mg ESR 1150 CL. The adverse events leading to interruption of the study were nausea and vomiting, especially in female subjects. A direct influence of ESR 1150 CL upon the pyloric sphincter can be taken into consideration as possible explanation for the dose-dependent adverse event pattern. There was no obvious dose-dependent pattern of any free-flow urometry parameter, which would have pointed to a dose-dependent increase in bladder sphincter tone of healthy subjects. This does not, however, exclude a potential influence upon pathologically decreased bladder sphincter tone. The pharmacokinetic results point to a rapid absorption of ESR 1150 and a rapid first-pass metabolism to CDBG 163.