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		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: ---				
Name of active ingredient: BIII 890 CL, crobenetine		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 30 December 2002	**Number:** 599.11	**Study period (years):** 01/02 – 04/02		

Title of study:	Pharmacokinetics of 50 mg desipramine daily, given orally over 7 days with and without concomitant administration of 175 mg crobenetine, given as a 6 hrs i.v. infusion (one hour loading dose directly followed by a five hours maintenance dose). A randomised, placebo controlled, single blind (for crobenetine), two-way cross over trial in healthy male subjects.
Investigator:	[redacted]
Study centre:	[redacted] Germany
Publication (reference):	Not applicable.
Clinical phase:	I
Objectives:	The objective of the present study was to assess the effect of a 6 hrs two-step intravenous infusion of crobenetine on the pharmacokinetics of desipramine (steady state) following oral administration of seven repeated doses of 50 mg once daily desipramine in healthy male volunteers.
Methodology:	Balanced, two-sequence, two-period, single-centre, open-label for desipramine, single blind for crobenetine, randomised, two-way crossover design
No. of subjects entered:	
total:	24 (20 completed)
each treatment:	24 (20 completed)
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 – 50 years, body mass index: 18.5 – 29.9 kg/m^2
Test product:	Desipramine tablet with crobenetine infusion
dose:	50 mg Desipramine (tablet) and 175 mg/6h crobenetine (5% mannitol solution)
mode of admin.:	Desipramine: Oral administration with 180 mL water crobenetine: 6 hrs two-step i.v. infusion (one hour loading dose (50 mg/h) + five hours maintenance dose (25 mg/h))
batch no.:	B000708 (BIII 890 CL) and S07200 (desipramine)
Duration of treatment:	7 days (p.o.) for desipramine, 6 hours (i.v. infusion) for crobenetine
Reference therapy:	Desipramine tablet and placebo infusion
dose:	50 mg desipramine (tablet) and 175 mg/6h placebo (5% mannitol solution)

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mode of admin.:	Desipramine: Oral administration with 180 mL water Placebo: 6 hrs two-step i.v. infusion (one hour loading dose + five hours maintenance dose)
batch no.:	B000704 (placebo) and S07200 (desipramine)
Criteria for evaluation:	
Efficacy:	***Pharmacokinetics*** *Primary endpoints:* $C_{max,ss}$ and AUC_{ss} of desipramine *Secondary endpoints:* individual time courses of the drug plasma concentrations, and pharmacokinetic parameters for desipramine and crobenetine
Safety:	Physical examination, vital signs (BP, PR), 12-lead ECG, clinical laboratory tests, adverse events and the evaluation of tolerability
Statistical methods:	Two-sided 95% CIs for expected median intra-subject (intra-individual) ratios of AUC_{ss} and $C_{max,ss}$ for desipramine with and without crobenetine and $AUC_{0-\infty}$, AUC_{0-tz} and C_{max} for crobenetine will be calculated. The statistical model will be ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs will be based on the residual error from ANOVA. Additionally, the corresponding point estimates will be provided. Descriptive statistics for all other parameters.
SUMMARY - CONCLUSIONS:	
Efficacy results:	***Pharmacokinetics*** There was, as seen in vitro, some evidence of a minor degree of inhibition of desipramine metabolism upon co-administration of crobenetine (95% confidence interval from 96.8 to 111% for $C_{max,ss}$ with a point estimate of 104% and from 99.9 to 117% for AUC_{ss} with a point estimate of 108%). However, the degrees of increase in $C_{max,ss}$ and AUC_{ss} were low and certainly much below the 30% limit specified as a clinically significant pharmacokinetic interaction for desipramine.

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Safety results:	There were no changes in vital signs (blood pressure/pulse rate, body temperature, respiratory rate), ECG and laboratory parameter, which could be related to a drug effect. A total of 83 adverse events were reported by 23 subjects. The most frequently reported adverse events were fatigue (14 subjects), somnolence (7 subjects), headache (6 subjects), palpitations (4 subjects), nausea (3 subjects), feeling cold (3 subjects), dizziness (3 subjects), nervousness (3 subjects), sleep disorder (3 subjects) and increased sweating (3 subjects). Nine subjects reported 10 adverse events of moderate intensity, one subjects had experienced an adverse event of severe intensity. All other adverse events were of mild intensity. Most adverse events observed post dose were attributable to desipramine and in accordance with its side effect profile. There were only four adverse events clearly associated with crobenetine administration (deafness, chest pain, injection site reaction and phlebitis). All other adverse events were also present after administration of desipramine alone or also occurred with placebo infusion.
Conclusions:	Crobenetine co-administration has been shown in this study to have no clinically relevant impact on steady-state desipramine pharmacokinetics. BIII 890 co-administered with desipramine was systemically well tolerated as judged from the assessment of vital signs, ECG, general safety laboratory and adverse event profiles. The incidence or severity of desipramine adverse events was not increased nor was the safety profile of BIII 890 including the potential to produce local reactions changed.