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: Not applicable				
Name of active ingredient: BIII 890 CL		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 6 Juni 2000	**Number:** 599.1	**Study period (years):** 04/99 – 12/99		

Title of study:	A single-blind, placebo-controlled, parallel group, single increasing dose tolerance study in healthy male volunteers after intravenous administration of BIII 890 CL (dosage: 0.5 mg/h – 80 mg/h), infusion time 1 hour.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Center Ingelheim, Boehringer Ingelheim Pharma KG, F.R.G.
Publication (reference):	not applicable
Clinical phase:	I
Objectives:	safety, tolerability and pharmacokinetics
Methodology:	single rising doses, single blind groups, placebo controlled, parallel group
No. of subjects entered:	
total:	88
each treatment:	six subjects (four on BIII 890 CL, two on placebo) on dose level D1 (0.5 mg/h), eight subjects (six on BIII 890 CL, two on placebo) on dose level D2 (2.5 mg/h), eight subjects (six on BIII 890 CL, two on placebo) on dose level D3 (5 mg/h), seven subjects (six on BIII 890 CL, one on placebo) on dose level D4 (10 mg/h), seven subjects (six on BIII 890 CL, one on placebo) on dose level D5 (20 mg/h), eight subjects (six on BIII 890 CL, two on placebo) on dose level D6 (30 mg/h), eight subjects (six on BIII 890 CL, two on placebo) on dose level D7 (40 mg/h), eight subjects (six on BIII 890 CL, two on placebo) on dose level D8 (50 mg/h), eight subjects (six on BIII 890 CL, two on placebo) on dose level D9 (60 mg/h), eight subjects (six on BIII 890 CL, two on placebo) on dose level D10 (70 mg/h); eight subjects, planned for dose level D11 (80 mg/h), were not treated due to premature termination of the trial, four subjects dropped out during the screening period.
Diagnosis and main criteria for inclusion:	healthy male volunteers, age 21 – 50 years, Broca-Index ± 20 %
Test product:	BIII 890 CL
dose:	single dose
mode of admin.:	intravenous infusion (duration – 1 hour)
batch no.:	B981203

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Duration of treatment:	one day at each dose level/subject
Reference therapy:	placebo
dose:	single dose
mode of admin.:	intravenous infusion (duration – 1 hour)
batch no.:	B981202
Criteria for evaluation:	
Efficacy:	not applicable
Safety:	blood pressure, pulse rate, ECG, respiratory rate, oral body temperature, laboratory tests, adverse events, pharmaco EEG, pharmacokinetics
Statistical methods:	descriptive statistics, ANOVA

SUMMARY - CONCLUSIONS:

Efficacy results, pharmacokinetic results:

Pharmacokinetics of BIII 890 BS in healthy male volunteers were determined after i.v. infusion (duration 1 hour) of 0.5, 2.5, 5, 10, 20, 30, 40, 50, 60 and 70 mg BIII 890 (doses refer to the amount of active ingredient of the drug, i.e. free base) administered as the hydrochloride BIII 890 CL. Plasma and urine concentrations were measured by a validated HPLC-MS/MS method. Pharmacokinetic parameters using non-compartmental methods were calculated for the 30, 40, 50, 60 and 70 mg doses. Only C_{max}, t_{max} and $AUC_{0\text{-}4\,h}$ were evaluated for doses ≤ 20 mg due to insufficient measurable plasma data at later time points (1.08-24 h) and a more frequent sampling in the terminal phase of doses >20 mg. In addition, data from the 30, 40 and 50 mg doses were fitted using a three-compartmental model.

Plasma concentrations increased rapidly to a maximum but did not reach steady state. Geometric mean plasma concentrations at maximum were 6.18 ng/ml (0.5 mg dose group), 36.0 ng/ml (2.5 mg dose group), 65 ng/ml (5 mg dose group), 133 ng/ml (10 mg dose group), 235 ng/ml (20 mg dose group), 301 ng/ml (30 mg dose group), 400 ng/ml (40 mg dose group), 594 ng/ml (50 mg dose group), 543 ng/ml (60 mg dose group) and 617 ng/ml (70 mg dose group).

Escalation to doses higher than 50 mg led to abnormal shapes of the plasma concentration-time profiles of the drug between 1 and 2 h after start of infusion and to AUC-values that did not increase compared to those calculated for the 40 and 50 mg dose groups. In comparison with doses ≤ 50 mg this points to a possibly altered pharmacokinetic and/or drug related behaviour of BIII 890 in doses of 60 and 70 mg.

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With non-compartmental analysis of the 30, 40, 50, 60 and 70 mg doses, MRT of disposition was in the range of 5.27-7.67 h (geom. mean). Total plasma clearance was between 730-1260 ml/min (geom. mean). Geometric mean V_{SS} (volume of distribution at steady state) was between 303-463 l. The geometric mean terminal half-life was in the range of 10.5-13.9 h. With compartmental analysis of the 30, 40 and 50 mg doses, geometric mean V_C (central compartment volume) was 9.02-15.7 l; the range of geometric mean half-life of the three phases of disposition and their partial areas under the curve were $t_{1/2}$ (b1) = 0.05-0.07 h (21.2-30.3 %), $t_{1/2}$ (b2) = 0.86-0.90 h (28.8-33.1 %) and $t_{1/2}$ (b3) = 12.4-13.1 h (39.3-41.4 %).

With respect to C_{max} and $AUC_{0\text{-}4\,h}$, pharmacokinetics of BIII 890 BS were dose proportional for doses from 0.5 mg (for C_{max}) and 2.5 mg (for $AUC_{0\text{-}4h}$) up to 30 mg. For doses > 30 mg there was an increase in a less than proportional manner with the dose.

The cumulative urinary excretion of BIII 890 in the 0-8 h fraction after infusion of 50 mg amounted 0.005 %-0.03 % of the dose. On this basis, renal excretion of the parent compound was assumed to be negligible and was therefore not further evaluated.

Summary table of BIII 890 pharmacokinetic parameters (non-compartmental analysis)

		30 mg		40 mg		50 mg		60 mg		70 mg	
		gmean	gCV (%)	gmean	gCV (%)	gmean	gCV (%)	gmean	gCV (%)	gmean	gCV (%)
$t_{1/2}$	[h]	10.5	19.0	10.6	15.7	11.1	17.1	12.7	62.1	13.9	12.2
MRT_{disp}	[h]	6.79	23.9	6.54	34.2	6.93	18.5	5.27	77.8	7.67	6.23
CL_{tot}	[ml/min]	753	30.6	800	14.9	730	16.3	1260	11.2	1010	17.5
V_{SS}	[l]	307	23.1	314	46.3	303	22.7	397	71.2	463	14.0

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Safety results:

The results of this single-centre, single-blind, placebo-controlled, randomised dose escalation study show that rising doses of 0.5 mg/h to 70 mg/h BIII 890 CL administered intravenously in 5 % Xylitol did not produce any clinically relevant changes in the vital parameters, EEG and standard safety laboratory parameters. Volunteer no. 77 (70 mg BIII 890 CL) showed a significant PQ-Prolongation in the ECG. Twenty-two of the 76 treated subjects reported adverse events.

There was evidence for a dose dependent increase in frequency and intensity of adverse events on treatment with BIII 890 CL. Also the quality of adverse events changed dose-dependently. Up to a dose of 40 mg/h no complaints about local tolerability were reported. At the dose of 50 mg/h "burning sensation at the infusion site" (1 report on BIII 890 CL) and "pain at the infusion site" (1 report on BIII 890 CL) occurred. At the dose of 60 mg/h one case of thrombophlebitis (1 report on BIII 890 CL) and at the dose of 70 mg/h two cases of thrombophlebitis (both on BIII 890 CL) were seen. In order to describe the symptoms of thrombophlebitis in a detailed manner these symptoms were reported separately. At dose level D9 (60 mg/h) volunteer [redacted] reported induration of the infusion vein, pain at the infusion site, reddening at the infusion site and tenderness along the course of the infusion vein. At dose level D10 (70 mg/h) volunteer [redacted] reported induration of the infusion vein, pain at the infusion site and tenderness along the course of the infusion vein, volunteer [redacted] reported induration of the infusion vein, pain at the infusion site and tenderness along the course of the infusion vein. The induration of the infusion vein was still present at the time of data base lock. Volunteer [redacted] reported burning sensation at the infusion site.

Therefore, based on the results of this study, the dose of 70 mg/h was well tolerated systemically whereas a 0.05 % solution (50 mg/h) was the locally maximum tolerated concentration in healthy volunteers.

Conclusions:

In conclusion due to the observations made in this study a 0.05 % BIII 890 CL solution can be described as the maximum tolerated concentration in healthy volunteers. Up to this concentration BIII 890 CL was free of any side effects which would raise objections to further clinical studies in volunteers or patients.