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: Not applicable				
Name of active ingredient: BIII 890 CL		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 17 September 2001	**Number:** 599.2	**Study period (years):** 01 – 09/2000		

Title of study:	A single blind, placebo-controlled, parallel-group, single increasing dose tolerance study in healthy young male volunteers after intravenous administration of BIII 890 CL as loading dose (dosage: 12.5, 25 and 50 mg/h, infusion time 1 hour; 50 mg/h, infusion time 2 hours) followed by maintenance dose (dosage: 6.25, 12.5 and 25 mg/h, infusion time 5 hours; 30 mg/h, infusion time 4 hours) and in healthy elderly male and female volunteers after intravenous administration of BIII 890 CL as loading dose (dosage: 50 mg/h, infusion time 1 hour) followed by maintenance dose (dosage: 25 mg/h, infusion time 5 hours).
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	Not applicable.
Clinical phase:	I
Objectives:	Safety, tolerability and pharmacokinetics of BIII 890.
Methodology:	Randomised, single blind, placebo-controlled, parallel-group
No. of subjects entered:	
total:	73
each treatment:	D_1: 11 young males, D_2: 14 young males, D_3: 12 young males; 14 elderly males, 14 elderly females, D_4: eight young males
Diagnosis and main criteria for inclusion:	healthy young male volunteers: age between 21 and 50 years, BROCA index ±20%; healthy elderly male and female volunteers: age >60 years, BROCA index ±25%.
Test product:	BIII 890 CL
dose:	D_1: 12.5 mg/1 h + 31.25 mg/5 h; D_2: 25 mg/1 h + 62.5 mg/5 h; D_3: 50 mg/1 h + 125 mg/5 h; D_4: 100 mg/2 h + 120 mg/4 h (doses refer to the amount of the active ingredient of the drug, i.e. free base)
mode of admin.:	intravenous infusion (duration – 6 hours)
batch no.:	B990914, B991207, B990913.
Duration of treatment:	one single dose/subject

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Reference therapy:	placebo
dose:	Dose scheme similar to test product
mode of admin.:	intravenous infusion (duration – 6 hours)
batch no.:	5% mannitol solution labelled as placebo: B990920, B991205. 5% mannitol solution for dilution purposes: B991003, B991205, B990920.
Criteria for evaluation:	
Efficacy:	not applicable
Safety:	Vital signs (blood pressure/pulse rate, body temperature, respiratory rate), ECG, adverse events, laboratory parameters, coagulation parameters, bleeding time
Pharmacokinetics:	C_{max}, t_{max}, $t_{½}$, AUC_{0-tf}, $AUC_{0-\infty}$, MRT, CL, V_Z, V_{SS}, Ae
Statistical methods:	descriptive analysis

SUMMARY - CONCLUSIONS:

Efficacy results: not applicable

Safety results: There were no changes in vital signs (blood pressure/pulse rate, body temperature, respiratory rate), ECG, laboratory parameter, coagulation parameter and bleeding time, which could be related to a drug effect. Adverse events observed post dose in subjects treated according to protocol were: injection site reaction (pain, 2/49), phlebitis (contralateral to the infusion site, 1/49), thrombophlebitis (3/49 and 1/17 placebo, due to late onset two cases, one after active and one after placebo treatment, were assigned to the post-treatment phase), fatigue (1/49 and 1/17 placebo), headache (9/49 and 3/17 placebo), dizziness (1/17 placebo), somnolence (8/49; only seen after the lowest dose), abdominal pain (2/49), diarrhoea (2/49 and 1/17 placebo), vomiting (1/49), arthralgia (1/49), dysuria (1/49). There was no indication for an increase in incidence and/or severity of adverse events with dose except for thrombophlebitis, which was clearly associated with the highest dose.

Seven subjects (five with active treatment and two with placebo treatment) were excluded from the statistical safety analysis because the study drug was not administered according to protocol and hence these subjects could not be assigned to one of the dose groups. Adverse events observed in these subjects were: phlebitis (contralateral to the infusion site, 1/5), thrombophlebitis (1/5) fatigue (1/5), influenza – like symptoms (1/49), headache (2/5 and 1/2 placebo) and vomiting (1/5).

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Pharmacokinetics:

Pharmacokinetics of BIII 890 in young healthy male volunteers were determined after 6 hours i.v. infusion of 43.75, 87.5 and 175 mg BIII 890 as a one hour loading dose directly followed by a five hours maintenance dose and 220 mg BIII 890 as a two hours loading dose directly followed by a four hours maintenance dose. In addition pharmacokinetics of BIII 890 in elderly healthy male and female volunteers was determined after 6 hours i.v. infusion of 175 mg BIII 890 as a one hour loading dose directly followed by a five hours maintenance dose. Although BIII 890 was administered as the hydrochloride BIII 890 CL, all doses refer to the amount of active ingredient of the drug, i.e. free base. Plasma and urine concentrations were measured by using a validated HPLC-MS/MS method. Pharmacokinetic parameters were calculated using non-compartmental methods. In addition, plasma data were fitted using a three-compartmental model.

By infusing BIII 890 as a 6 hours two-step i.v. infusion to young male, elderly male and female volunteers, plasma concentrations increased rapidly to a maximum at the end of the one respectively two hours loading dose. After changing the infusion rate from loading to maintenance dose, BIII 890 concentrations decreased to a minimum and than started to increase again up to the end of infusion. Especially while infusing the five hours maintenance dose of the 43.75, 87.5 and 175 mg dose groups, BIII 890 plasma-concentration time profiles do not increased regularly as expected, they showed some irregularities in form of humps and kinks being more pronounced for elderly volunteers. Because of this, the interindividual variability of the plasma concentrations was something higher for elderly volunteers, particularly for elderly females. Such irregularities in the plasma concentration-time profiles were not seen during the four hours maintenance dose of the 220 mg dose group.

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With non-compartmental analysis MRT of disposition (MRT_{disp}) for young male was in the range of 5.5-7.7 h (geom. mean) and for elderly male and female 8.5 and 11.0 h (geom. mean). Total plasma clearance (CL_{tot}) in young male was between 673-801 mL/min (geom. mean) and in elderly male and female 760 and 685 mL/min (geom. mean). Geometric mean volume of distribution at steady state (V_{SS}) in young male was between 257-339 l and in elderly male and female 389 and 451 l. The geometric mean terminal half-life in young male was in the range of 10.6-13.7 h and in elderly male and female 13.8 and 17.3 h.

In general, non-compartmental pharmacokinetic parameters calculated for young males after infusing BIII 890 as a 1 h (study 599.1, [U00-1628]) or as a 6 h i.v. infusion were in good agreement.

Due to the difficulties in properly fitting a compartmental model to the data, especially the data of the maintenance dose of the 43.75, 87.5 and 175 mg/6 h dose groups, the pharmacokinetic parameters MRT_{disp}, CL_{tot} and V_{SS}, evaluated by three-compartmental analysis were in the same range but something different to the ones calculated by non-compartmental methods.

For young male volunteers, variability at AUC_{0-tf} (CV = 15.6 to 18.3) and $AUC_{0-\infty}$ (CV = 16.5 to 21.5) was moderate, and kinetics of BIII 890 were dose proportional with respect to AUC_{0-tf} and $AUC_{0-\infty}$.

Pairwise comparisons between the groups young males, elderly males and elderly females did not reveal differences for the parameter AUC_{0-tf}. For $AUC_{0-\infty}$ the confidence intervals for the comparisons elderly females/elderly males and elderly females/young males exceed the upper limit of the acceptance range of 125%. Since only one dose was tested in elderly volunteers, the number of evaluable elderly females was low and the plasma concentrations in elderly volunteers, especially in elderly females, was highly variable, the gender effect shown by a pairwise comparison between groups of $AUC_{0-\infty}$ should be interpreted with caution.

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Conclusions:

The systemic tolerability of BIII 890 was good at all dose levels tested as judged from the assessment of vital signs, ECG, general safety laboratory and coagulation data and adverse event evaluation. The occurrence of dizziness in all subjects treated with BIII 890 at the lowest dose and the absence of this adverse event at all higher doses is not explainable solely on the basis of the available data.

Local tolerability was judged as good at lower doses despite sporadic pain at the infusion site. At the highest dose level (220 mg) thrombophlebitis occurred in the majority of subjects treated with active drug. Also, the subject overdosed with 350 mg (nominal) developed thrombophlebitis at the infusion site.
In young male subjects, both parameters, AUC_{0-tf} and $AUC_{0-\infty}$, increased in proportion with the dose.

Pairwise comparisons between the groups young males, elderly males and elderly females did not reveal differences for the parameter AUC_{0-tf}. For $AUC_{0-\infty}$ the point estimates for the comparisons elderly females/elderly males and elderly females/young males were slightly higher than 100%; and the respective confidence intervals exceeded the upper limit of the acceptance range of 125%. However, since the sample sizes were relatively small, the gender effect of $AUC_{0-\infty}$ shown by the pairwise comparison between groups should be interpreted with due caution. This minor difference in male and female subjects seen with $AUC_{0-\infty}$ is regarded not to be relevant.