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: BIIR 561 CL		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 19 November 2002	**Number:** 600.6	**Study period (years):** 08 – 09/2000		

Title of study:	A single-blind, placebo-controlled single dose tolerance study in healthy elderly male and female volunteers after intravenous administration of BIIR 561 CL as loading dose (dosage: 75 mg/h, infusion time 1 hour) followed by maintenance dose (dosage: 40 mg/h and 75 mg/h, infusion time 5 hours)
Investigator:	[redacted]
Study center(s):	[redacted] Germany
Publication (reference):	None
Clinical phase:	I
Objectives:	Safety, tolerability and pharmacokinetics in elderly
Methodology:	Single rising dose, single-blind groups, placebo-controlled
No. of subjects entered:	
total:	13
each treatment:	9 active (275 mg BIIR 561), 4 placebo
Diagnosis and main criteria for inclusion:	Healthy female and male volunteers, age ≥ 60 years, Broca-Index: ± 25 %
Test product:	BIIR 561 CL
dose:	75 mg/1 h + 200 mg/5 h (40 mg/h); total dose: 275 mg
mode of admin.:	Intravenous infusion
batch no.:	B990510
Duration of treatment:	One single infusion over 6 hours
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Intravenous infusion
batch no.:	B990509
Criteria for evaluation:	
Efficacy:	Not applicable
Safety:	Blood pressure, pulse rate, ECG, respiratory rate, oral body temperature, bleeding time, laboratory parameters, adverse events, pharmacokinetics
Statistical methods:	Descriptive analysis

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SUMMARY - CONCLUSIONS:

Pharmacokinetic results:

Pharmacokinetics of BIIR 561 in elderly healthy male and female volunteers were determined after 6 hours i.v. infusion of 275 mg BIIR 561 as a 1 hour loading dose directly followed by a five hours maintenance dose (all doses refer to the amount of active ingredient of the drug, i.e. free base) administered as the hydrochloride BIIR 561 CL. Plasma and urine concentrations were measured by using validated UV-HPLC methods. Pharmacokinetic parameters were calculated using non-compartmental methods. In addition, data from all subjects were fitted using a three compartmental model.

During the infusion, plasma concentrations rapidly increased to a maximum at the end of the loading dose. After changing the infusion from loading to maintenance dose, BIIR 561 levels decreased to a minimum and started to increase again upon the end of the infusion. Geometric mean plasma concentrations at maximum at the end of infusion (end of the five hours maintenance dose) were 286 ng/ml (elderly male) and 296 ng/ml (elderly female).

With non-compartmental analysis mean residance time of disposition (MRT_{disp}) was 8.59 h (geom. mean, elderly male) and 8.77 h (geom. mean, elderly female). Total plasma clearance (CL_{tot}) was 1450 ml/min (geom. mean, elderly male) and 1460 ml/min (geom. mean, elderly female). Geometric mean V_{ss} (volume of distribution at steady state) was 745 l (elderly male) and 766 l (elderly female). The geometric mean terminal half-life was 7.80 h (elderly male) and 8.78 h (elderly female). With three-compartmental analysis the pharmacokinetic parameters CL_{tot}, V_{ss} and MRT_{disp} were comparabele to the ones calculated by non-compartmental analysis. The mean of V_C (central compartment volume) was 78.8 l (elderly male) and 69.2 l (elderly female); the range of mean half-life of the three phases of disposition and their partial areas under the curve for elderly male were $t_{1/2}(b1)$ = 2.78 min (6.05%), $t_{1/2}(b2)$ = 1.18 h (25.9%) and $t_{1/2}(b3)$ = 8.96 h (68.1%) and for elderly female $t_{1/2}(b1)$ = 3.65 min (9.80%), $t_{1/2}(b2)$ = 1.55 h (28.7%) and $t_{1/2}(b3)$ = 9.98 h (61.5%).

The cumulative urinary excretion of BIIR 561 amounted to 0.12-0.24 % (geom. mean) of the dose in elderly males and 0.14-0.23 % (geom. mean) of the dose in elderly females.

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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. A minor effect was observed in the orthostatic reaction, i.e. compared with placebo a decrease in blood pressure and increase in pulse rate. Adverse events observed post dose were: dry mouth (1/9), fatigue (5/9), headache (3/9 and 1/4 placebo), malaise (1/9), dizziness (1/9), dysaesthesia (1/9), tachycardia (1/9).

One subject experienced a severe circulatory failure at the end of infusion. This event was considered as immediately life-threatening. As a consequence of this serious adverse event the study was terminated.

Conclusions:

BIII 890 plasma concentrations in elderly male and female volunteers were in the same range and showed no apparent differences. Even BIII 890 plasma concentrations in the volunteer which developed a serious cardiovascular failure were comparable to the ones of all the other volunteers and showed no abnormalities until the time point onset of adverse event.

Based on the adverse event profile, vital signs, ECG, standard safety laboratory parameters, coagulation parameters and signs of local tolerability the dose regimen (75 mg/1 h followed by 200 mg/5 h) was generally well tolerated by elderly subjects. There was, however, a tendency to orthostatic dysregulation shown as a relative decrease in systolic and diastolic blood pressure after two minutes standing and a marked simultaneous increase in pulse rate.

The occurrence of a serious cardiovascular failure in one subject could not be explained by an individual disposition of the subject. The event happened suddenly without any clear prodromal signs and can be explained as the intensified reaction of the cardiovascular system known from animal pharmacology. With the current knowledge it is not possible to define a safe dose at which cardiovascular incidents can be ruled out.