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: BIIR 561 CL		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 12 October 2001	**Number:** 600.2	**Study period (years):** 11/99 – 06/00		

Title of study:	A single blind, placebo-controlled single increasing dose tolerance study in healthy male volunteers after intravenous administration of BIIR 561 CL as loading dose (dosage: 37.5 mg/h – 150 mg/h, infusion time 1 hour) followed by maintenance dose (dosage: 20 mg/h – 40 to 125 mg/h, infusion time 5 hours)
Investigator:	[redacted]
Study centre(s):	Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, Germany
Publication (reference):	not applicable
Clinical phase:	I
Objectives:	safety, tolerability and pharmacokinetics
Methodology:	randomised, single rising doses, single blind groups, placebo-controlled
No. of subjects entered:	
total:	60
each treatment:	placebo – 15; BIIR 561 CL: 137.5 mg/6 h – 9; 275 mg/6 h – 9; 350 mg/6 h – 9; 375 mg/6 h – 9; 450 mg/6 h – 9 (for details see section 6.1)
Diagnosis and main criteria for inclusion:	healthy male volunteers, age 21 – 50 years, Broca-Index ± 20 %
Test product:	BIIR 561 CL
dose:	137.5 mg/6 h, 275 mg/6 h, 350 mg/6 h, 375 mg/6 h, 450 mg/6 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.:	B990510
Duration of treatment:	one day at each dose level/subject
Reference therapy:	placebo
dose:	single dose
mode of admin.:	intravenous infusion (duration – 6 hours)
batch no.:	B980804

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Criteria for evaluation:

Efficacy:	AUC, C_{max}, t_{max}, A_e, MRT, $t_{1/2}$ and CL, V_{ss}
Safety:	blood pressure, pulse rate, ECG, respiratory rate, oral body temperature, laboratory tests, adverse events, pharmacokinetics

Statistical methods: descriptive statistics, ANOVA

SUMMARY - CONCLUSIONS:

Pharmacokinetic results:

Pharmacokinetics of BIIR 561 in young healthy male volunteers were determined after 6 hours i.v. infusion of 137.5, 275, 350 and 375 mg BIIR 561 as a 1 hour loading dose directly followed by a five hours maintenance dose and a 6 hours continuous iv. infusion of 450 mg BIIR 561 (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 except from subject [redacted] and [redacted] of the 375 mg/6h dose group were fitted using a three compartmental model. Although data from a 1 hour intravenous infusion of increasing doses of BIIR 561 in young healthy male volunteers (study 600.1; [U00-1297]) and from most of the subjects of this study point to a three-compartmental model as the most appropriate one, plasma concentration data from subject [redacted] and [redacted] could, however, only be fitted to a two-compartmental model.

During the infusion of 137.5, 275, 350 and 375 mg/6 h BIIR 561, plasma concentrations increased rapidly 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 159 ng/mL (137.5 mg/6h dose group), 312 ng/mL (275 mg/6h dose group), 368 ng/mL (350 mg/6 h dose group) and 376 ng/mL (375 mg/ 6h dose group). While infusing the five hours maintenance dose the plasma concentration-time profiles showed some irregularities in form of humps and kinks. Pharmacokinetic characteristics of BIIR 561, the high volume of distribution and the very high plasma clearance of the drug, in addition to rapid changes in the volumes of the body fluids, by changing the position of the subjects and changes in liver blood flow by food uptake may be the reason for these irregularities.

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Pharmacokinetic results (continued):

While continuously infusing 450 mg/6h BIIR 561, plasma levels increased to a maximum (498 ng/mL; geom. mean) but did not reach steady state. With non-compartmental analysis MRT of disposition (MRT_{disp}) was in the range of 5.01-7.25 h (geom. mean). Total plasma clearance (CL_{tot}) was between 1510-1810 mL/min (geom. mean). Geometric mean V_{SS} (volume of distribution at steady state) was between 521-731 L. The geometric mean terminal half-life was in the range of 5.38-7.27 h. With three-compartmental analysis (excluding subjects [redacted] and [redacted] from the 375 mg/6 dose group) the pharmacokinetic parameters CL_{tot}, V_{ss} and MRT_{disp} were comparable to the ones calculated by non-compartmental analysis. The geometric mean of V_C (central compartment volume) was between 56.6-82.1 L; the range of geometric mean half-life of the three phases of disposition and their partial areas under the curve were $t_{1/2}(b1)$ = 2.49-4.67 min (8.42-14.5%), $t_{1/2}$ (b2) = 1.06-1.67 h (33.4-41.0%) and $t_{1/2}(b3)$ = 6.47-9.11 h (42.0-54.1%).

With respect to $AUC_{0\text{-}tf}$ and $AUC_{0\text{-}\infty}$, pharmacokinetics of BIIR 561 was dose proportional indicating linear pharmacokinetics of BIIR 561.

The cumulative urinary excretion of BIIR 561 amounted to 0.1-0.3% (mean) of the dose and the renal clearance was in the range of 1.67-4.21 mL/min (geom. mean).

Summary table of BIIR 561 pharmacokinetic parameters (non-compartmental analysis)

		137.5 mg/6h		275 mg/6 h		350 mg/6 h		375 mg/6 h		450 mg/6 h	
		gmean	gCV (%)	gmean	gCV (%)	gmean	gCV (%)	gmean	gCV (%)	gmean	gCV (%)
$t_{1/2}$	[h]	5.38	28.4	5.57	34.1	6.99	19.1	7.27	15.2	6.00	24.9
MRT_{disp}	[h]	5.01	31.9	5.20	32.5	5.80	23.3	7.25	13.5	5.45	17.9
CL_{tot}	[mL/min]	1730	30.5	1730	27.8	1510	11.8	1680	12.1	1810	21.6
V_Z	[l]	807	14.1	831	27.4	912	17.7	1060	19.5	9.40	16.6
V_{SS}	[l]	521	15.4	538	22.6	524	23.9	731	15.0	592	14.8
CL_{ren}	[mL/min]	1.67	48.8	2.54	58.7	2.02	96.0	4.21	79.0	3.04	52.8

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Safety results:

There was evidence for a dose dependent increase in frequency and intensity of adverse events on treatment with BIIR 561 CL, in particular for those, which were already suggested as pharmacodynamic effects by the preclinical profile of the compound. Also the nature of adverse events exacerbated treatment- and dose-dependently.

Beginning at the second dose level D_2 of 275 mg/6h "somnolence" was the most frequent adverse events (32 reports on BIIR 561 CL) followed by "conjunctivitis" (26 reports on BIIR 561 CL beginning at the third dose level D_3 of 350 mg/6h), " muscle contraction involuntary " (10 reports on BIIR 561 CL most frequent and beginning at 350 mg/6h), "mouth dry" (nine reports on BIIR 561 CL beginning at 275 mg/6h), "vertigo" (eight reports beginning at dose level D_4 375 mg/6h), "psychosis" (four reports at 350mg/6h and 375 mg/6h), "hypotension postural" (four reports on BIIR 561 CL beginning at 350 mg/6h),"nausea" (three reports at 350 mg/6h and at dose level D_5 450mg/6h) and "anxiety" (two reports on BIIR 561 CL beginning at 375 mg/6h). "Stupor" was reported once and "speech disorder" was reported twice at 350mg/6h, "emotional lability" was reported twice and "syncope" was reported once at 375mg/6h. For 15 subjects the local adverse events summarised as "injection site reaction" were observed.

Three main issues appeared in the overall pattern of these adverse events:

The local tolerability was poor as observed with the higher total dose (dose level D_2). However, the local tolerability was improved concerning frequency, intensity and duration of the phlebitis for the 0.1 % solution. For the systemic tolerability two different patterns could be observed. The highest loading dose of 150 ml/h resulted in more pronounced 'somnolence' Although the dose levels D_3 and D_4 are comparably high, the intensity of AEs characterised by disturbed vigilance ('somnolence', 'stupor') was more pronounced at dose level D_3 (total dose 350 mg/6 h) compared with D_4 (total dose 375 mg/6 h), probably caused by the higher loading dose. On the other hand the amount of total dose seemed to have influence on the regulation of the circulation. Beginning with D_3 some subjects complained of 'postural hypotension' in the pharmacodynamic model 'orthostatic testing' seven hours after the start of infusion.

Conclusions:

In conclusion, due to the observations made in this study over the dose range of 137.5 mg/6h to 450 mg/6 h and with the treatment regimen applied in this trial BIIR 561 CL was safe. Nevertheless, the tolerability appeared to be diminished in two ways: 1. local tolerability was not acceptable when the drug concentration in the solution for infusion was as high as 0.2 %; 2. systemic tolerability was not acceptable due to considerably reduced consciousness with a loading dose of 150 mg/h. Furthermore, systemic tolerability appeared to be reduced at the end of infusion (beginning wit a total dose of 350 mg/6 h), as few subjects showed disturbed regulation of blood pressure and pulse rate as seen by orthostatic testing. Safety parameters blood pressure, pulse rate (with the exception of BP and PR in orthostatic testing in some subjects), respiratory rate, body temperature, EEG, ECG and standard laboratory tests did not reveal any obvious clinically significant drug-related changes. On the basis of the results of this study within the limitations pointed out above BIIR 561 CL was free of any side effects which would raise objections to further clinical studies in volunteers or patients.