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: 2 February 2000	**Number:** 600.1	**Study period (years):** 01/99 – 08/99		

Title of study:	A single-blind, placebo-controlled single increasing dose tolerance study in healthy male volunteers after intravenous administration of BIIR 561 CL (dosage: 1 mg/h – 175 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:	randomised, single-blind, placebo-controlled, parallel group
No. of subjects entered:	
total:	84
each treatment:	eight subjects (six on BIIR 561 CL, two on placebo) on dose level D1 (1mg/h), D2 (3 mg/h), D3 (7.5 mg/h), D5 (30 mg/h), D6 (45 mg/h), D7 (66 mg/h), D9 (125 mg/h) and D11 (175 mg/h), seven subjects (five on BIIR 561 CL, two on placebo) on dose level D8 (100 mg/h) and D10 (150 mg/h), six subjects (five on BIIR 561 CL, one on placebo) on dose level D4 (15 mg/h). Doses refer to the amount of active ingredient of the drug, i.e. free base.
Diagnosis and main criteria for inclusion:	healthy male volunteers, age 21 – 50 years, Broca-Index ± 20 %
Test product:	BIIR 561 CL
dose:	single dose
mode of admin.:	intravenous infusion (duration – 1 hour)
batch no.:	B980805
Duration of treatment:	one day at each dose level/subject
Reference therapy:	placebo
dose:	single dose

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mode of admin.:	intravenous infusion (duration – 1 hour)
batch no.:	B980804
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, pharmaco EEG, pharmacokinetics
Statistical methods:	descriptive statistics, ANOVA

SUMMARY - CONCLUSIONS:

Efficacy results pharmacokinetic results:

Pharmacokinetics of BIIR 561 BS in healthy male volunteers were determined after i.v. infusion (duration 1 hour) of 1, 3, 7.5, 15, 30, 45, 66, 100, 125, 150 and 175 mg BIIR 561 (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 validated UV-HPLC methods. Pharmacokinetic parameters were calculated using non-compartmental methods. In addition, data from the 125, 150 and 175 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 2.88 ng/ml (1 mg dose group), 9.41 ng/ml (3 mg dose group), 20.1 ng/ml (7.5 mg dose group), 25.9 ng/ml (15 mg dose group), 78.4 ng/ml (30 mg dose group), 117 ng/ml (45 mg dose group),160 ng/ml (66 mg dose group), 203 ng/ml (100 mg dose group), 477 ng/ml (125 mg dose group), 513 ng/ml (150 mg dose group) and 577 ng/ml (175 mg dose group). With non-compartmental analysis of the 1 mg to 175 mg doses, MRT of disposition was 6.08 h (geom. mean). Total plasma clearance was 1940 ml /min (geom. mean). Geometric mean V_{SS} (volume of distribution at steady state) was 708 l. The geometric mean terminal half-life was 6.87 h. With compartmental analysis of the 125, 150 and 175 mg doses, geometric mean V_C (central compartment volume) was 61.7 l; the geometric mean half-life of the three phases of disposition and their partial areas under the curve were $t_{1/2}$ (b1) = 0.09 h (18.5 %), $t_{1/2}$ (b2) = 1.8 h (34.6 %) and $t_{1/2}$ (b3) = 10.6 h (44.7 %).

Plasma concentrations increased essentially in proportion with the dose indicating linear pharmacokinetics of BIIR 561 BS.

The cumulative urinary excretion of BIIR 561 BS amounted to 0.08 % – 0.25 % (mean) of the dose.

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Summary table of BIIR 561 BS pharmacokinetic parameters (geom. mean; non-compartmental analysis)

1 mg - 175 mg	$t_{½}$ [h]	MRT_{disp} [h]	CL_{tot} [ml/min]	V_z [l]	V_{ss} [l]
N	49	49	49	49	49
mean	7.08	6.35	2040	1190	742
CV (%)	22.8	28.0	33.1	27.8	34.2
median	7.41	6.34	1840	1080	640
min	3.63	2.83	1020	694	410
max	9.64	10.3	4020	2190	1710
gmean	6.87	6.08	1940	1150	708
gCV (%)	26.5	32.1	32.4	26.5	30.0

Source Data: section 14, TABLE 14.4: 2

Safety results:

The results of this single-centre, single-blind, placebo controlled, randomised dose escalation study show that rising doses of 1 mg/h to 175 mg/h BIIR 561 CL administered intravenously in 0.9 % NaCl solution did not produce any clinically relevant changes in the vital parameters ECG, EEG and standard safety laboratory parameters. Twenty-four of the 84 treated subjects reported adverse events.

There was evidence for a dose dependent increase in frequency and intensity of adverse events on treatment with BIIR 561 CL which were suggested as pharmacodynamic effects by the preclinical profile of the compound. Also the quality of adverse events changed dose-dependently (cf. section 12.2.1, 12.2.2, 12.2.3). Beginning at the dose of 30 mg/h "fatigue" was the most frequent adverse events (20 reports on BIIR 561 CL) followed by "somnolence" ("drowsiness", 12 reports on BIIR 561 CL beginning at 125 mg/h), "speech disorder" ("slurred speech", 6 reports on BIIR 561 CL beginning at 150 mg/h) and "psychosis" ("lightheadedness", 5 reports on BIIR 561 CL beginning at 125 mg/h). In the highest dose of 175 mg/h "nystagmus" (4 reports), "vertigo" (3 reports), "anxiety" ("apprehensiveness", 2 reports) and "apathy" (1 report) were reported. Also "mouth dry" was observed in the highest dose of 175 mg/h (5 reports on BIIR 561 CL). This adverse event can be interpreted as anticholinergic effect which was either peripherally or centrally driven. Due to the observations made in this study it can be concluded that beginning with the dose of 150 mg/h adverse events may occur which are driven by the cerebellum ("slurred speech" at 150 mg/h, "vertigo" and "nystagus" at 175 mg/h). Therefore, based on the results of this study the dose of 150 mg/h can be described as the maximum tolerated dose in healthy volunteers.

Conclusions:

In conclusion, due to the observations made in this study the dose of 150 mg/h can be described as the maximum tolerated dose in healthy volunteers. Up to this dose level BIIR 561 CL was free of any side effects which would raise objections to further clinical studies in volunteers or patients.