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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Not applicable				
Name of active ingredient: BIBP 5371 CL		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 15 Feb 2006	**Number:** U06-1123	**Study period (dates):** 20 Apr 04 – 06 Aug 04		

Title of study:	Safety, tolerability and pharmacokinetics of BIBP 5371 CL following oral administration to healthy male and female volunteers (dose range: 10 – 350 mg). A double-blind (within treatment groups), randomised, placebo-controlled, single rising dose study, including comparisons of 50 mg vs. 100 mg tablet and tablet vs. drinking solution, and investigation of food effect.
Investigator:	[redacted]
Study center:	Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	Date of this study has not been published
Clinical phase:	I
Objectives:	Safety, tolerability and pharmacokinetics (including comparisons of different formulations and investigation of food effect)
Methodology:	Double-blind (within treatment groups), randomised, placebo-controlled, single oral rising doses, comparisons of 50 mg vs. 100 mg tablet and tablet vs. drinking solution, investigation of food effect
No. of subjects:	
planned:	70
actual:	70 Treatment A: BIBP 5371 CL tablets entered: 62 treated: 62 analysed (for primary endpoint): 62 Treatment B: BIBP 5371 drinking solutions entered: 8 treated: 8 analysed (for primary endpoint): 8
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age 21 – 50 years, bodymass index (BMI): 18.5 – 29.9 kg/m^2
Test product:	BIBP 5371 CL tablets (at one dose level also drinking solution)
dose:	10, 30, 60, 100, 150, 200, 250, 300, 350 mg
mode of admin.:	oral
batch no.:	B040118 (10 mg), B040201 (50 mg), B040305 (100 mg), B040219 (150 mg)
Duration of treatment:	Single doses of BIBP 5371 CL (maximum two single doses separated by at least 4 weeks)

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Reference therapy:	Placebo tablets (at one dose level also drinking solution)
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B040112 (10 mg), B040117 (50 mg), B040116 (100 mg), B040221 (150 mg), B040220 (Solvent)
Criteria for evaluation:	
Efficacy:	Pharmacokinetic parameters: C_{max}, t_{max}, $AUC_{0-\infty}$, $\%AUC_{0-tz}$, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$
Safety:	Vital signs (blood pressure, pulse rate, respiratory rate, body temperature), electrocardiogram, laboratory parameters, adverse events (including findings in medical examination), global tolerability assessment
Statistical methods:	Descriptive statistics in general, parametric ANOVA/ANCOVA methods for log-transformed pharmacokinetic parameters

SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics

Starting with an orally given dose of 30 mg BIBP 5371 CL plasma concentrations were measurable in all treated subjects. After dosages of either 120 or 150 mg, the threshold peak exposure concentration of 205 ng/mL, which was based on the NOAEL (phospholipidosis) in cynomolgus monkeys, was exceeded in 5/6 and 6/6 volunteers, respectively.

There was a steep increase in the total and maximum exposure after raising the dose from 100 to 120 mg (gMean $AUC_{0-\infty}$ and C_{max} increased from 453 ng*h/mL and 117 ng/mL to 840 ng*h/mL and 292 ng/mL, respectively). In some individuals a high intra-individual variability within the first 4 hours after drug intake became obvious. Despite the same dose of 100 mg and essentially the same conditions, AUC_{0-4} differed by up to 189 %. Concomitant intake of a high fat, high calorie meal led to a remarkable drop in oral bioavailability at a dose of 30 mg BIBP 5371 CL. The gMean C_{max} was reduced by 86% when comparing the exposure after drug intake in the fasted vs. the fed state.

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Safety results:	In this study all 70 study subjects tolerated a single dose of BIBL 5371 CL as tablet or drinking solution well in a dose range of 10 mg up to 150 mg orally without serious adverse events. 8 subjects reported a total of 10 adverse events and 4 of these 10 adverse events were assessed as related to study drug. With the exception of one severe cytomegalovirus infection, all other adverse events were mild to moderate. A dose relation of adverse events was not observed. The study was not powered to detect tolerability and safety differences in solid versus soluble study drug application or fasted versus study drug intake with meal. The most frequent adverse event related to study drug was headache which can be explained by BIBP 5371 mechanism of action as CGRP receptor antagonist. Safety relevant findings according to physical examination, ECG and laboratory analyses were not obtained.
Conclusions:	In conclusion, non-linear kinetics, intra-individual variability and a pronounced food effect together with a limited dose range (upper dose-limit of 100 mg) were regarded as major disadvantages for further development of BIBP 5371 CL. Major safety concerns for this study drug were not raised