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: BIIF 1149 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 11 May 2001	**Number:** 1157.2	**Study period (years):** 3/99 – 7/99		

Title of study:	A single increasing dose safety, tolerability and pharmacodynamics (citric acid challenge) study after oral administration of BIIF 1149 BS (drinking solution, single doses: 0.1 – 25 mg; in addition, at 25 mg also as a 25 mg tablet) in healthy young male volunteers (randomised, double-blind, placebo-controlled, parallel groups)
Investigator:	[redacted]
Study centres:	Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, FRG
Publication (reference):	Data of the trial has not been published
Clinical phase:	I
Objectives:	Safety, tolerability, pharmacodynamics and pharmacokinetics
Methodology:	Randomised, double-blind, placebo-controlled, parallel group
No. of subjects entered:	
total:	Sixty-four (64; eight groups each of eight subjects)
each treatment:	Eight subjects (six on BIIF 1149 BS, two on placebo) per each of the eight dose levels; two study days at dose levels 0.1-17.5 mg (day 1: safety and tolerability, day 2 (eight days after day 1): citric acid challenge); three study days at dose level 25 mg (day 3: treatment with a 25 mg tablet; eight days after day 2).
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 – 50 years, Broca-Index $\pm$ 20 %
Test product:	BIIF 1149 BS oral drinking solution and a BIIF 1149 BS 25 mg tablet
dose:	Single doses: 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 17.5, 25 mg of BIIF 1149 BS
mode of admin.:	Oral administration
batch no.:	B990107 (solution); B990511 (tablet)
Duration of treatment:	Two days at one dose level / subject (one without and one with citric acid challenge); in addition at 25 mg a third test day with a 25 mg tablet
Reference therapy:	BIIF 1149 BS placebo solution and a BIIF 1149 BS placebo tablet
dose:	Not applicable
mode of admin.:	Oral administration
batch no.:	B990106 (solution); B990515 (tablet)

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Criteria for evaluation:

Efficacy:	Not applicable
Safety:	Blood pressure, pulse rate, ECG, adverse events, laboratory tests, pharmacokinetics
Pharmacokinetics:	AUC, C_{max}, t_{max}, A_e, MRT, $t_{½}$ and CL/F
Statistical methods:	Descriptive analysis, ANOVA, confidence intervals

SUMMARY – CONCLUSIONS:

Efficacy results:

Not applicable

Safety results:

The results of this single-centre, double-blind (within dose levels), placebo controlled, randomised study show that increasing doses of 0.1 to 25 mg BIIF 1149 BS (as drinking solution and as a 25 mg tablet) did not produce any clinically relevant changes in the vital parameters, ECG and standard safety laboratory parameters.

Sixty-two male subjects were treated and completed the study according to the protocol. Six (one of them on placebo) of 62 treated subjects reported eight adverse events.

The most frequent adverse event was headache (three subjects on active drug).

Three adverse events were of moderate intensity and five adverse events were of mild intensity. There was no evidence of a drug-related increase in frequency or intensity of adverse events.

All adverse events were regarded as not drug-related.

It is concluded, that BIIF 1149 BS was well tolerated in all dose groups.

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Pharmacokinetic results:

In plasma the pharmacologically active metabolite BIIF 1148 BS is the predominant compound with a slower elimination phase compared to the parent compound BIIF 1149 BS. Plasma concentrations of both compounds increased quickly (median t_{max} = 0.75 h – 4 h) after administration of either solution or tablet. The mean terminal half-life of BIIF 1148 BS and BIIF 1149 BS was estimated consistently between 44 to 59 hours and between 6 to 9 hours, respectively. Mean C_{max} of BIIF 1149 BS and BIIF 1148 BS at 25 mg (tablet) dose level was 37 ng/mL and 74 ng/mL, respectively. Highest plasma concentrations (C_{max}) were observed at 113 ng/mL for BIIF 1148 BS and at 65 ng/mL for BIIF 1149 BS. The interindividual variability with respect to C_{max}, AUC_{0-24h} and $AUC_{0-\infty}$ was moderate (BIIF 1148 BS: range of 12.3 % – 41.1 % gCV; BIIF 1149 BS: range of 26.2 % – 73.6 % gCV). In average urinary excretion of BIIF 1149 BS and BIIF 1148 BS was about 0.15 % and 7 % of dose, respectively. The parameters C_{max}, AUC_{0-24h}, and $AUC_{0-\infty}$ increased in proportion with the dose (0.1 mg – 25 mg) for both substances, BIIF 1149 BS and BIIF 1148 BS. The relative bioavailability of the tablet was comparable to the drinking solution (25 mg) with regard to C_{max}, AUC_{0-24h}, and $AUC_{0-\infty}$ for BIIF 1149 BS and BIIF 1148 BS.

Pharmacodynamics results:

The citric acid challenge showed no antitussive effect of BIIF 1149 BS after single dosing.

Conclusions:

BIIF 1149 BS administered as single oral doses (as drinking solution and in addition at 25 mg as a tablet) over a dose range from 0.1 to 25 mg was well tolerated. BIIF 1148 BS is the predominant compound in plasma reflecting an extensive first pass metabolism of BIIF 1149 BS. BIIF 1149 BS and BIIF 1148 showed dose proportionality from 0.1 to 25 mg. The tablet formulation is nearly equivalent to the drinking solution and recommended to be used in further trials. Urinary excretion of BIIF 1149 BS and BIIF 1148 BS is of minor relevance.