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: not applicable				
Name of active ingredient: BIIF 1149 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 24 October 2001	**Number:** 1157.3	**Study period (years):** 11/99 – 06/00		

Title of study:	A double-blind (within dose groups), randomised, placebo-controlled, parallel-group study to investigate the safety, tolerability and preliminary pharmacokinetics of increasing repeated oral doses (nine days treatment of 5 mg and 10 mg and eighteen days treatment of 25 mg and 40 mg) of BIIF 1149 BS in healthy male volunteers
Investigator:	[redacted]
Study centre:	[redacted] Germany
Publication (reference):	Data of this trial has not been published
Clinical phase:	I
Objectives:	Safety, tolerability and preliminary pharmacokinetics following repeated administration
Methodology:	Randomised, double-blind within dose groups, placebo-controlled, parallel groups
No. of subjects entered:	
total:	Forty-eight (48, four groups each of 12 subjects)
each treatment:	Twelve subjects (nine on BIIF 1149 BS, three on placebo) per each of the four dose levels.
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 – 50 years, Broca-Index ±20%
Test product:	BIIF 1149 BS tablets at 5 mg and 25 mg
dose:	Four doses: 5 mg, 10 mg, 25 mg and 40 mg of BIIF 1149 BS
mode of admin.:	Oral administration
batch no.:	B990704 and B991203 (5 mg); B990511 and B991206 (25 mg)
Duration of treatment:	Nine study days (q.i.d. dosing of the respective dose on day 1 and once daily dosing of the respective dose on days 2-9) for groups 1 and 2 and eighteen study days (daily dosing of the respective dose on days 1-18) for groups 3 and 4
Reference therapy:	BIIF 1149 BS matching placebo tablets
dose:	Not applicable
mode of admin.:	Oral administration
batch no.:	B990805 (5 mg) and B990515 (25 mg)

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Criteria for evaluation:

Efficacy:	Not applicable
Safety:	Blood pressure, pulse rate, ECG, adverse events, laboratory tests; preliminary pharmacokinetics following repeated administration
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 groups), randomised, placebo-controlled study show that increasing repeated oral doses of 5 mg to 40 mg BIIF 1149 BS administered in two different dose regimens did not produce clinically relevant changes in the vital parameters, 12-lead ECG and most standard safety laboratory parameters of healthy male volunteers. The investigator judged the global tolerability to be good. However, elevated liver values, mainly SGPT, were observed frequently.

Twenty-two of 48 treated subjects reported 37 adverse events. In 19 subjects the adverse events were judged as mild and in three subjects as moderate in intensity. No subject experienced an adverse event of severe intensity.

The most common adverse events were gastro-intestinal complaints (N = 10) and general disorders (eight occurrences of headache and two cases of abdominal pain). Significant increases (up to four times the upper limit of normal) in hepatic enzymes - mainly SGPT- which were classified as adverse events occurred in four subjects.

However, a total of 19 subjects showed at least on one occasion an elevated SGPT; three, four, five and seven subjects in the respective four dose groups. Out of these 19 subjects four had received placebo; one in each dose group (verum-placebo ratio for SGPT increases 2:1, 3:1, 4:1 and 6:1 for the four dose levels, respectively; verum-placebo-ratio for medication 9:3, i.e. 3:1 in all dose groups).

Subject # [redacted] had considerably increased SGPT values during the trial, which were classified as significant adverse event by the investigator. These values lead to withdrawal of this subject from the trial after the 12th dose. Subsequently the medication code was broken for this subject and revealed that he had received 40 mg BIIF 1149 BS.

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Subject # [redacted] developed an extreme CK increase with concomitant rise in SGPT, SGOT and LDH during treatment, which required discontinuation of treatment and hospitalisation. By definition this case was classified as serious adverse event. Emergency unblinding revealed that the subject had received placebo.

With the exception of the liver enzyme abnormalities and one case of flatulence all adverse events were judged as not drug-related by the investigator.

Considering the number of subjects showing increased liver values, the comparison of the verum-placebo ratio of SGPT increases with the verum-placebo ratio of the medication (3:1) and the magnitude of enzyme elevations, the changes in SGPT values in the lower dose groups (5 mg and 10 mg) can most probably be attributed to hospitalisation. However, a drug relationship cannot be excluded, especially because the treatment phase was only nine days.

The more evident SGPT alterations - in terms of magnitude, frequency and verum-placebo ratio - in the upper dose groups (25 mg and 40 mg) point to a probable dose-dependent drug effect. Moreover, increased GLDH values in some subjects confirm a possible hepatotoxic potential of BIIF 1149 BS and/or BIIF 1148 BS, at least at higher repeated oral doses of BIIF 1149 BS. However, a possible hospitalisation effect - at least as contributing factor - cannot be excluded.

Although elevations in liver values appeared to be dose-dependent no clear relation to plasma concentrations of BIIF 1149 BS or the metabolite BIIF 1148 BS could be found in subjects showing marked effects.

There was no pattern in the frequency of the remaining adverse events, which would suggest a clear relation to treatment or dose level. However, dyspepsia and flatulence were reported only on treatment and only in the two highest dose groups.

Pharmacokinetics:

In plasma the metabolite BIIF 1148 BS is the predominant compound on day 1 and on the last treatment day 9/18 at steady state with a slower elimination phase compared to the parent compound BIIF 1149 BS. The mean terminal half-life of BIIF 1148 BS and BIIF 1149 BS was estimated consistently between 64 to 75 hours and between 7 to 10 hours, respectively. Mean $C_{max,ss}$ of BIIF 1149 BS and BIIF 1148 BS at 40 mg dose level was 406 ng/mL and 95.5 ng/mL, respectively. Highest plasma concentrations at steady state $C_{max,ss}$ were observed at 558 ng/mL for BIIF 1148 BS (25 mg dose) and 150 ng/mL for BIIF 1149 BS (40 mg dose), respectively. Maximum plasma concentrations for the metabolite BIIF 1148 BS were achieved quickly (median t_{max} = 3 h) at all dose levels on day 1 and day 9/day 18. For the parent compound BIIF 1149 BS maximum plasma concentrations appeared even faster with median t_{max} = 1 h after drug intake on day 1 and day 9/day18. The interindividual variability with respect to $C_{max,ss}$ and $AUC_{ss,\ 0\text{-}24h}$ was moderate to high (BIIF 1148 BS: range of 15.1% - 41.7% gCV; BIIF 1149 BS: range 26.5% - 73.4% gCV). If $C_{max,ss}$ and

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$AUC_{ss\ 0\text{-}24h}$ is considered, plasma concentrations of parent compound BIIF 1149 BS represented up to around 20% and 9%, respectively, of those of the metabolite BIIF 1148 BS. BIIF 1149 BS showed no remarkable accumulation factor to steady state which was around 1.26 and 1.35 for C_{max} and AUC, respectively. In contrast BIIF 1148 BS showed considerable increase in pre-dose plasma levels after multiple dosing of BIIF 1149 BS with an accumulation factor which was around 3.06 and 3.73 for C_{max} and AUC, respectively. It is indicated that after once daily dosing of BIIF 1149 BS steady state is commonly reached after day 10 for BIIF 1148 BS and after day 2 for BIIF 1149 BS and that dose proportionality can be assumed in the dose range from 5 mg to 40 mg BIIF 1149 BS.

Conclusions:

The pharmacokinetic results of this study (5 - 40 mg) are similar and consistent to those obtained in the first single rising dose studies (0.1 - 100 mg). BIIF 1148 BS is the predominant compound in plasma reflecting an extensive first pass metabolism of BIIF 1149 BS. For a once daily dosing regimen a treatment of at least 10 days is necessary to achieve steady state conditions with an approximately 3.5 fold increase of BIIF 1148 BS plasma levels.

Increasing repeated oral doses of 5 mg to 40 mg BIIF 1149 BS administered in two different dose regimens did not produce clinically relevant changes in the vital parameters, 12-lead ECG and most standard safety laboratory parameters of healthy male volunteers. The investigator judged the global tolerability to be good.

However, elevated liver values, mainly SGPT, were observed frequently and appeared to be dose-dependent. They led to the withdrawal of one subject receiving 40 mg BIIF 1149 BS after the 12^{th} dose. Increased GLDH values in some subjects confirm a possible hepatotoxic potential of BIIF 1149 BS and/or BIIF 1148 BS, at least at higher repeated oral doses of BIIF 1149 BS. However, a possible hospitalisation effect - at least as contributing factor - cannot be excluded.