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: BIIL 284 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 13 October 2000	**Number:** 543.4	**Study period (years):** 07/99 to 09/99		

Title of study:	A double-blind, randomised, placebo-controlled, parallel-group study to investigate the safety, tolerability, biological effects and preliminary pharmacokinetics of increasing repeated oral doses (9 days dosing) of BIIL 284 BS (doses: 25 mg, 150 mg, 250 mg as WIF tablets) in healthy male volunteers.
Investigator:	[redacted]
Study centre(s):	Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, F.R.G.
Publication (reference):	not applicable
Clinical phase:	I
Objectives:	safety, tolerability, surrogate marker CD11b (= Mac -1) and preliminary pharmacokinetics following repeated administration
Methodology:	randomised, double-blind within dose groups, placebo-controlled, parallel groups
No. of subjects entered:	
total:	35
each treatment:	11 subjects (9 on BIIL 284 BS, 2 on placebo) in the lowest dose group, 12 subjects (9 on BIIL 284 BS, 3 on placebo) in the two higher dose groups, 9 study days per each dose level
Diagnosis and main criteria for inclusion:	healthy male volunteers, age 21 - 50 years, Broca-Index: ± 20%
Test product:	BIIL 284 BS tablets
dose:	three doses: 25 mg, 150 mg and 250 mg of BIIL 284 BS
mode of admin.:	oral after standard breakfast
batch no.:	B990104 (25 mg), B990105 (75 mg)
Duration of treatment:	nine days at each dose level / subject
Reference therapy:	BIIL 284 BS placebo tablets
dose:	not applicable
mode of admin.:	oral after standard breakfast
batch no.:	B990312 (25 mg), B990206 (75 mg)

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Criteria for evaluation:

Efficacy: surrogate marker: 'inhibition of in vitro LTB_4 induced CD11b (= Mac -1) expression'

Safety: blood pressure, pulse rate, respiratory rate, ECG, adverse events, laboratory tests, preliminary pharmacokinetics (test of steady state, accumulation factor) following repeated administration

Statistical methods: descriptive analysis

SUMMARY - CONCLUSIONS:

Safety results:

Due to the observations made in this study and described in this report BIIL 284 BS was safe and predominantly well tolerated in healthy male volunteers following multiple doses of 25 mg, 150 mg and 250 mg BIIL 284 BS. Safety parameters blood pressure, pulse rate, body temperature, ECG and standard laboratory tests did not reveal any obvious clinically significant drug-related changes. There was no evidence for a dose dependent increase in either frequency or intensity of adverse events. Eleven of the 27 subjects who received the active drug experienced 16 AEs of mild to moderate intensity. All AEs were transient in nature. The most frequent AE was fatigue (seven subjects, five on active drug, two on placebo). The results of this single-centre, double-blind, placebo-controlled, randomised (within dose groups) multiple dose escalation study show that the specific surrogate marker 'LTB_4 induced Mac-1 expression' was considerably to completely inhibited at all doses starting on day 1 and lasted at least 24 h after the last treatment on day 9. From comparison of time course of plasma concentrations and IME, a long-lasting dynamic effect was seen consistently even when plasma concentrations declined to very low values (24 h after administration). The extent and duration of action appears more pronounced at the higher doses.

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Other results:

The results of this single-centre, double-blind, placebo-controlled, randomised (within dose groups) multiple dose escalation study show that the specific surrogate marker 'LTB_4 induced Mac-1 expression' was considerably to completely inhibited at all doses starting on day 1 and lasted at least 24 h after the last treatment on day 9. From comparison of time course of plasma concentrations and IME, a long-lasting dynamic effect was seen consistently even when plasma concentrations declined to very low values (24 h after administration). The extent and duration of action appears more pronounced at the higher doses.

BIIL 284 BS administered as WIF tablet once daily for nine days under fed conditions showed dose- proportionality from 25 mg to 250 mg with respect to pharmacokinetic parameters C_{max} and AUC of BIIL 315 ZW and BIIL 304 ZW (main metabolites of BIIL 284 BS in plasma). Steady state was achieved at day 3-4 after first dosing for BIIL 315 ZW and BIIL 304 ZW. For BIIL 315 ZW the average accumulation to steady state is about 1.3. Time to reach C_{max} at steady state was in average 3 h. Highest C_{max} of BIIL 315 ZW was observed with 172 ng/mL. The inter-subject variability at steady state with respect to $C_{max,ss}$ and AUC_{ss} of BIIL 315 ZW was in the range 38.5% - 79.8% gCV. The estimated terminal half-life of BIIL 315 ZW at steady state ranged from 19.3 h to 24.1 h which is comparable to estimates after single oral dosing. The average renal excretion was about 0.008 % for BIIL 315 ZW and 0.0005 % of dose for BIIL 304 ZW indicating that urinary excretion is of minor relevance.

Conclusions:

BIIL 284 BS was safe and well tolerated in all dose groups. With the dosage regimen administered in this trial BIIL 284 BS was free of any side effects which would raise objections to further clinical studies in volunteers or patients.

The specific surrogate marker 'LTB_4 induced Mac-1 expression' was considerably to completely inhibited at all doses starting on day 1 and lasted at least 24 h after the last treatment on day 9. BIIL 284 BS showed dose proportionality from 25 mg to 250 mg. Steady state was reached after 3-4 days. BIIL 315 ZW accumulates to steady state by a factor of about 1.3. Urinary excretion of BIIL 284 BS and its metabolites is of minor relevance (less than 0.01 % of dose).