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***.

3. SYNOPSIS AND TRIAL ABSTRACT

3.1 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: BIIL 284 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:** I of VII	**Page:** 1	**to** BC 16	**Addendum No.:**
Report date: 9 June 1999	**Number:** 543.1	**Study period (years):** 7/98 – 12/98		

Title of study:	A double-blind, randomised, placebo-controlled, parallel-group study to investigate the safety, tolerability, biological effects and preliminary pharmacokinetics of increasing single oral doses of BIIL 284 BS (dose range: 0.025 mg - 75 mg PSE solution, 25 mg, 75 mg, 250 mg and 750 mg WIF tablets) in healthy male volunteers as well as food effects at 75 mg (WIF tablet).
Investigators:	[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), white blood cells and preliminary pharmacokinetics as well as preliminary data on food effect (at the dose of 75 mg WIF tablet)
Methodology:	randomised, double-blind within dose groups, placebo-controlled, parallel groups
No. of subjects:	
total:	95
each treatment:	eight subjects (six on BIIL 284 BS, two on placebo) per each of the twelve dose groups, one study day per each dose level (exception: D_9 (75 mg WIF tablet); five on BIIL 284 BS, two on placebo)
Diagnosis and main criteria for inclusion:	healthy male volunteers, age 21 – 50 years, Broca-Index: ± 20 %
Test product:	BIIL 284 BS oral solution, PSE 1 %
dose:	single doses: 0.025, 0.25, 0.75, 2.5, 7.5, 25, 75 mg of BIIL 284 BS
mode of admin.:	oral
batch no.:	B980213 (0.025 mg), B980213 (0.25 mg), B980214 (0.75 mg), B980211 (2.5 mg), B980217 (7.5 mg), B980218 (25 mg), B980404 (75 mg)
Test product:	BIIL 284 BS WIF tablets
dose:	single doses: 25, 75, 250, 750 and 75 mg (fed) of BIIL 284 BS
mode of admin.:	oral
batch no.:	B980611 (25 mg), B980701 (75 mg)

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Duration of treatment:	one day at each dose level / subject
Reference therapy:	BIIL 284 PSE placebo solution
dose:	not applicable
mode of admin.:	oral
batch no.:	B980227 (0.025mg), B980227 (0.25 mg), B980226 (0.75 mg), B980225 (2.5 mg), B980224 (7.5 mg), B980215 (25 mg), B980405 (75 mg)
Reference therapy:	BIIL 284 BS placebo tablets
dose:	not applicable
mode of admin.:	oral
batch no.:	B980703 (25 mg), B980702 (75 mg)
Criteria for efficacy:	not applicable
Criteria for safety:	clinical examination including blood pressure, pulse rate, ECG, adverse events, laboratory tests; surrogate marker CD11b (= Mac -1), white blood cells, preliminary pharmacokinetics
Statistical methods:	descriptive analysis

SUMMARY – CONCLUSIONS:

Safety results:
The oral administration of BIIL 284 BS given as PSE formulation up to 75 mg and given as WIF tablet up to 750 mg as well as given as 75 mg WIF tablet after standard breakfast was safe and well tolerated. Five drug-related adverse events of mild to moderate intensity were observed in 95 treated subjects (three on BIIL 284 BS, two on placebo). There was no evidence of a dose dependent increase in frequency or intensity of adverse events. Neither measurements of vital parameters (i.e. blood pressure, pulse rate) nor ECG and standard laboratory evaluation did reveal any clinical significant changes.

Dose response relationship:
The administered doses of BIIL 284 BS as PSE solution ranging from 0.025 mg to 75 mg covered the total range of response from ' no effect' to complete 'inhibition of LTB4 induced Mac-1 expression' even 24 hours following drug administration (25 mg and 75 mg doses). Complete inhibition was also achieved following oral doses of 25 mg, 75 mg, 250 mg, and 750 mg as WIF tablet. Graphical representations of mean response-time profiles show that the inhibition was complete until 24 hours following administration of BIIL 284 BS as 250 mg and 750 mg WIF tablet in fasted state and as 75 mg WIF tablet in fed state.

Name of company: Boehringer Ingelheim Pharma KG		**Tabulated Study Report SUPPLEMENTARY SHEET**		**(For National Authority Use only)**
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SUMMARY – CONCLUSIONS:

Pharmacokinetics:
The main metabolite in plasma after oral administration of BIIL 284 BS was BIIL 315 ZW.
A clear food effect was observed with the 75 mg WIF tablet as compared to 75 mg WIF tablet fasted showing higher bioavailability (approx. factor of 3 in C_{max} and AUC) with later t_{max} and decreased inter-subject variability with respect to model-free pharmacokinetic parameters.
Geometric mean values for terminal half-life ranged from 15.5 to 32.7 h.
The PSE treatments showed a slightly over-proportional bioavailability with increasing doses, whereas the WIF tablets showed full dose proportionality.
Urinary excretion of BIIL 284 BS and its metabolites BIIL 260 BS and BIIL 315 ZW accounted for less than 0.04 % of the dose administered.

Conclusions:
In conclusion, BIIL 284 BS administered orally is safe and well tolerated. The clinical findings of this single dose study confirm that the compund can be safely administered to humans without producing adverse events or clinical findings which could raise objections to further clinical trials. Maximum pharmacodynamic effect (% 'inhibition of LTB_4 induced Mac-1 expression') over 24 hours was observed with PSE doses $\geq$ 25 mg, with WIF tablet doses $\geq$ 250 mg (fasted) and with the 75 mg WIF tablet given in fed state. Peak plasma concentrations of BIIL 315 ZW above 10 to 20 ng/ml appear to prolomg complete inhibition up to 24 h following administration of BIIL 284 BS. Administration of 75 mg WIF tablets together with a standard breakfast appears to lower the variability of absorption and to increase the bioavailability compared to administration of WIF tablets in fasted state. Geometric mean values for terminal half-life ranged from 15.5 to 32.7 hours. Urinary excretion of BIIL 284 BS and its metabolites accounted for less than 0.04 % of the dose administered.