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: n.a.				
Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 14 July 2000	**Number:** 1175.1	**Study period (years):** 1999		

Title of study:	Safety, pharmacokinetics and pharmacodynamics of single rising doses (1, 4, 15, 50, 100, 200, 400, and 600 mg) oral BIRB 796 BS in healthy human subjects. A placebo controlled, randomised study, double blinded at each dose level
Investigator:	[redacted]
Study centre(s):	Human Pharmacology Centre, Biberach an der Riss, Germany
Publication (reference):	not yet published
Clinical phase:	I
Objectives:	To assess safety, pharmacokinetics and pharmacodynamics of BIRB 796 BS 1. In escalating single doses 2. With and without a 64 g fat breakfast at one selected dose
Methodology:	1. Single escalating dose, randomised, placebo controlled, blinded at each dose level 2. Food effect: single dose, randomised, intra-individual comparison
No. of subjects entered:	
total:	64 male
each treatment:	6 (BIRB 796 BS) plus 2 (placebo)
Diagnosis and main criteria for inclusion:	healthy male subjects, age 18 to 45 years
Test product:	BIRB 796 BS in 5 ml polyethylene glycol 400 (PEG 400) solution (1, 4, 15, 50, 100 mg doses) BIRB 796 BS in 10 ml PEG 400 solution (200, 400 mg doses) BIRB 796 BS in 15 ml PEG 400 solution (600 mg dose)
dose:	1. 1, 4, 15, 50, 100, 200, 400, 600 mg BIRB 796 BS (single dose escalating study) 2. 50 mg BIRB 796 BS (single dose food effect study)
mode of admin.:	*per os*
batch no.:	BIRB 796 BS: PD-1931, PD-1932, PD-1933, PD-1935, PD-1936, PD-1937, PD-1939, PD-1940 PEG 400: PD-1938, PD-1942
Duration of treatment:	single dose

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Reference therapy:	PEG 400
dose:	5 ml (for 1, 4, 15, 50, 100 mg dose levels) 10 ml (for 200, 400 mg dose levels) 15 ml (600 mg dose level)
mode of admin.:	*per os*
batch no.:	PD-1938, PD-1942
Criteria for evaluation:	
Efficacy / Pharmacokinetics:	Primary endpoints: safety and tolerability Secondary endpoints: pharmacokinetics (plasma concentration-time profiles of BIRB 796 BS, exploratory pharmacokinetics), pharmacodynamics (exploratory assessment of *in vitro* neutrophil activation, *ex vivo* endotoxin stimulation)
Safety:	Adverse events; tolerability; vital signs; routine laboratory values, white blood cell counts, exploratory safety markers
Statistical methods:	Descriptive statistics

SUMMARY - CONCLUSIONS:

Efficacy results:

Ex vivo Endotoxin-Induced TNFα Production Assay

The whole blood was stimulated with endotoxin in a proof of concept assay to determine if BIRB 796 BS would inhibit TNFα production in an *ex vivo* setting. Select time points (prior to dosing, and 2, 4, 6, 24, and 48 hours post dosing) were chosen. A summary of the results demonstrates that BIRB 796 BS, dosed at 400 and 600 mg, maximally inhibited TNFα production by approximately 42% and 62% with a trend towards increased extent and duration of inhibition with increasing doses.

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	Ex vivo Neutrophil Activation Assay (Mac-1/L-selectin cell surface marker ratio) Whole blood was stimulated with either fMLP or TNFα in a proof of concept assay to determine if BIRB 796 BS would activate neutrophil in an *ex vivo* setting. Neutrophil activation state was determined by the ratio of Mac-1/L-selectin expression measured by mean fluorescence intensity. Select times points (prior to dosing, and 4, 8, 24 and 48 hours post dosing) were chosen. (TNFα stimulation was only used for the 200, 400 and 600-mg dose). With fMLP as the stimulus, BIRB 796 BS, dosed at 200, 400, and 600 mg, maximally inhibited neutrophil activation by 43%, 60%, and 47%, respectively. With TNFα as the stimulus, BIRB 796 BS, dosed at 200, 400 and 600 mg, maximally inhibited neutrophil activation by 69%, 64% and 80%, respectively with a trend towards increased extent and duration of inhibition with increasing doses. *Effect and plasma concentration relationship:* An E_{max} model was found adequate in describing the concentration-effect relationship. The *ex -vivo* neutrophil activation with TNFα stimulation was most sensitive to the inhibition achieved by BIRB 796 BS with an EC_{50} of 91.5 ng/ml, followed by the *ex vivo* neutrophil activation with fMLP stimulation (237.7 ng/ml), and then by *ex vivo* LPS-induced TNFα production (1228 ng/ml).
Pharmacokinetics	Following oral administration absorption of BIRB 796 BS was rapid. Mean peak concentrations (C_{max}) occurred approximately within 1 to 2 hours after administration, and seemed to increase in the higher dose groups. A distinct absorption phase was observed after C_{max}, followed by a slower elimination phase with a half-life of approximately 8 hours. A significant food effect was found on both t_{max} and C_{max}, but not on $AUC_{0-\infty}$. C_{max} appeared to be slightly less than dose proportional at the highest dose, while dose-proportionality was observed for $AUC_{0-\infty}$. Inter-individual variability was moderate with a coefficient of variation of approximately 30% based on the $AUC_{0-\infty}$ values. Urinary excretion of intact BIRB 796 BS was negligible, accounting for only 0.02% of dose.

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Safety results:	BIRB 796 BS was associated with a small, clinically insignificant increase in γ-GT at single doses of at least 400 mg in 10 to 15 ml of PEG 400. The solvent, PEG 400, was associated with a slight, clinically insignificant increase in total bilirubin when administered as a single dose of 15 ml. BIRB 796 BS was well tolerated in healthy human males in single doses up to 600 mg when administered orally as a solution in PEG 400. Laboratory studies to assess for vasculitis (increase in white cell count, increase in baseline MAC-/L-selectin ratio) or endothelial damage (soluble IL-2, thrombomodulin, and factor VII associated antigen) showed no significant change from baseline or between treatment groups. Physical examination and vital signs were unremarkable. There was no evidence of retinitis by ophthalmologic examination. There were no clinically significant adverse events that could be attributed to either BIRB 796 BS or the vehicle PEG 400.
Conclusions:	It is concluded that BIRB 796 BS is well tolerated as single doses up to 600 mg in up to 15 ml of PEG 400 with an acceptable pharmacokinetic profile and potential pharmacodynamic effect as measured by various *ex vivo* models. BIRB 796 BS is suitable for further investigation. . If 15 ml or greater of PEG 400 is used in future studies as a single dose, bilirubin should be assessed. γ-GT should also be assessed in future studies of BIRB 796 BS at doses greater than 200 mg as a single dose.