Clinical Study Synopsis for Public Disclosure

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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:				
Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 18 June 2001	**Number:**	**Study period (years):** 03-07/2000		

Title of study:	Safety, pharmacokinetics and pharmacodynamics of BIRB 796 BS tablets (20, 50, 150, 300, and 600 mg) administered orally to healthy human subjects once daily for 7 days. A placebo controlled, randomised, double blinded study
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Biberach an der Riss, Germany
Publication (reference):	not as yet published
Clinical phase:	I
Objectives:	To assess safety, pharmacokinetics and pharmacodynamics of BIRB 796 BS 1. In escalating multiple doses 2. With and without a 64 g fat breakfast at the 50 mg dose level
Methodology:	1. Multiple dose: escalating after each dose group, randomised, double blinded, placebo controlled 2. Food effect: intra-individual comparison during a dosing interval of multiple dosing protocol at one dose level
No. of subjects entered:	
total:	24
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 tablets: 20 mg, 50 mg, 100 mg
dose:	1. 50 mg (1 x 50 mg), 150 mg (1 x 50 mg + 1 x 100 mg), 300 mg (3 x 100 mg), 600 mg (6 x 100 mg) BIRB 796 BS, 20 mg (1 x 20 mg) BIRB 796 BS (multiple escalating dose); 300 and 600 mg doses not given 2. 50 mg (1 x 50 mg) BIRB 796 BS (food effect)
mode of admin.:	*per os*
batch no.:	PD-1962, PD-1963, PD-1964
Duration of treatment:	7 days
Reference therapy:	placebo tablets matching 20, 50, and 100 mg active tablets

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Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
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dose:	1. 50 mg placebo (1 x 50 mg placebo), 150 mg placebo (1 x 50 mg placebo + 1 x 100 mg placebo), 300 mg placebo (3 x 100 mg placebo), 600 mg placebo (6 x 100 mg placebo), 20 mg (1 x 20 mg placebo); 300 and 600 mg placebo doses not given 2. 50 mg placebo (1 x 50 mg placebo)
mode of admin.:	*per os*
batch no.:	PD-1965, PD-1966, PD-1967
Criteria for evaluation:	
Efficacy / Pharmacokinetics:	Secondary endpoints: pharmacokinetics (plasma concentration-time profiles of BIRB 796 BS, pharmacokinetic parameters), pharmacodynamics (exploratory assessment of *ex vivo* neutrophil and monocyte activation with fMLP and tumour necrosis factor(TNF)α stimulation, *ex vivo* TNFα production with endotoxin stimulation, Multitest® assessment of cellular immunity)
Safety:	Primary endpoints: safety and tolerability (Adverse events; tolerability; vital signs; routine laboratory values, white blood cell counts, exploratory safety markers)
Statistical methods:	Descriptive statistics

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Ref. to Documentation:	**Volume:**	**Page:** **to**		**Addendum No.:**
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SUMMARY - CONCLUSIONS:

Efficacy results:

Two pharmacodynamic surrogate markers were developed using human whole blood to examine the effects of multiple dosing of BIRB 796 BS. These markers were *ex vivo* lipopolysaccharide (LPS) stimulated TNFα production and *ex vivo* fMLP or TNFα stimulated neutrophil activation. These tests were not designed for statistical examination instead they were designed to determine descriptive trends in the data.

In whole blood stimulated with LPS, TNFα production in volunteers treated with BIRB 796 BS at 20, 50, and 150 mg was not inhibited after 7 days of dosing.

In whole blood either unstimulated or stimulated with either fMLP or TNFα, BIRB 796 BS had multiple effects. No effect was evident at 20 mg, a decrease in Mac-1/L-selectin ratio at both trough and peak levels was demonstrated at 50 mg, and an increase in Mac-1/L-selectin ratio at trough levels and a decrease at peak levels was observed at 150 mg.

More specifically, BIRB 796 BS resulted in a decrease in Mac-1/L-selectin ratio at the 4 hr time point in a dose response manner with no response observed at the 20 mg dose, a modest effect at 50 mg, and a more pronounced inhibition at 150 mg. It is obviously from the 4 hr time point that BIRB 796 BS demonstrates a direct effect on inhibiting the Mac-1/L-selectin ratio, thus indicating a decrease in the activation state of neutrophils. These results are similar to those observed in the 1175.1 trial, however the response is more pronounced with multiple dosing.

However, this suggested direct response of BIRB 796 BS at 4 hr on neutrophil activation deviates at the 24 hr time point. Prior to dosing on day 7, BIRB 796 BS when dosed at 50 mg resulted in a decrease in the ratio of Mac-1/L-selectin as compared to placebo, possibly due to the long term actions of BIRB 796 BS on neutrophils. However, the 150 mg dose does not follow suit, demonstrating a clear increase in the ratio as compared to placebo, which may indicate an increase in the activation state of neutrophils. This finding is surprising due to the overwhelming evidence both *in vitro* and *in vivo* that BIRB 796 BS inhibits the ratio and thus neutrophil activation. Therefore, it is possible that with multi-dosing at 150 mg, an indirect effect is activating neutrophils at the 24 hr time point, which overrides the direct actions of BIRB 796 BS on inhibiting neutrophils.

BIRB 796 BS in doses up to 150 mg daily for 7 days does not have an effect on cellular immunity as measured by a change in response to the Multitest®.

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Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 18 June 2001	**Number:**	**Study period (years):** 03-07/2000		

Pharmacokinetic results	Following oral administration of the tablet dosage form, the absorption of BIRB 796 BS was rapid. Mean peak concentrations (C_{max}) occurred approximately within 1.5 hours after dose, both on days 1 and 7. A distinct distribution phase was observed after C_{max}, followed by a slower elimination phase with a half life of approximately 8 hours. Steady state was attained within 48 hours of multiple dosing. Area under the curve, peak and trough plasma concentrations were on average higher at steady state than on day 1. No food effect was found on any of the steady state pharmacokinetic parameters for the tablet dosage form. A high peak to trough ratio was observed from the once daily dosing schedule. Steady state C_{max} appeared to be dose proportional whereas $AUC_{0-\tau}$ was more than dose proportional. Inter-individual variability was moderately high, with a coefficient of variation of approximately 50% based on the $AUC_{0-\tau}$ values.
Safety results:	All subjects administered BIRB 796 BS completed the protocol. Subjects receiving 150 mg BIRB 796 BS daily for 7 days had moderate elevations in AST and ALT. Transaminase levels peaked 2 to 4 days after the end of drug therapy on day 7 with resolution over the next 7 to 14 days. The 150 mg BIRB 796 BS dose group also had a small increase in γ-GT. Two of six members of this dose group developed spontaneously resolving acne 2 days after the last drug administration. Because of these findings, 150 mg BIRB 796 BS for 7 days was not considered well tolerated and subsequent administration of the drug at 300 and 600 mg were cancelled. Doses of 20 and 50 mg daily for 7 days were well tolerated with no adverse events reported and no laboratory safety abnormalities other than a small increase in ALT and AST in 2 of 6 subjects receiving 50 mg BIRB 796 BS. None of the laboratory findings in this study were correlated with clinical abnormalities. Transaminase levels were higher with increasing dose. It is not known whether the toxicity was related to the maximum level of drug achieved or to the total cumulative hepatic exposure. The mechanism of elevation of transaminases was also unclear. There were no laboratory or clinical findings of vasculitis in this study. There was no increase in WBC, acute phase reactants, markers of endothelial damage, changes in urinalysis, or consistent physical findings, including complete ophthalmologic examination. No clinically relevant changes in lipase, amylase, or red cell morphology, or increase in QT intervals on EKG were demonstrated.

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Conclusions:	In whole blood stimulated with LPS, TNFα production was not inhibited by BIRB 796 BS at 20, 50, and 150 mg in volunteers after 7 days of dosing. In addition, BIRB 796 BS had no effect on neutrophil activation at 20 mg, showed a trend toward inhibiting neutrophil activation at 50 mg, and at 150 mg, demonstrated a trend toward activating neutrophil at trough levels but toward inhibiting activation 4 hours post dosing. BIRB 796 BS in doses up to 150 mg daily for 7 days does not have an effect on cellular immunity as measured by a change in response to the Multitest®. No food effect was found on any of the steady state pharmacokinetic parameters for the tablet dosage form. A high peak to trough ratio was observed from the once daily dosing schedule. Steady state $C_{max,ss}$ appeared to be dose proportional, whereas $AUC_{0-\tau}$ was more than dose proportional. Two of 6 subjects in the 150 mg dose group developed acne. BIRB 796 BS when administered at doses above 50 mg once daily for 7 days is associated with a moderate, clinically reversible, asymptomatic elevation in hepatic transaminases. Doses up to 50 mg once daily for 7 days were well tolerated.