Clinical Study Synopsis for Public Disclosure

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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.

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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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:				
Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
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Report date: 27 AUG 2003	**Number:** U03-1548	**Study period (dates):** 04 MAR 02 – 05 NOV 02		

Title of study:	Safety and pharmacokinetics of BIRB 796 BS tablets administered twice daily orally (total daily dose 90, 120, 150 or 180 mg) to healthy human subjects for 14 days. A placebo-controlled, dose escalation study double blinded at each dose level.
Investigators:	[redacted]
Study center:	[redacted]
Publication (reference):	Data of this study has not been published
Clinical phase:	I
Objectives:	To assess the safety and pharmacokinetics of BIRB 796 BS tablets administered as multiple daily doses at various dose levels
Methodology:	Multiple dose, placebo controlled, randomised, dose escalation study, double blinded for placebo. The conduct of each dose escalation depended on preceding transaminase results
No. of subjects:	
planned:	entered: 96 (per amendment:120)
actual:	entered: 120 Treatment A (BIRB 796 BS): entered: 80 (16 at each dose level), treated: 80 analysed (for primary endpoint): 80. Treatment B (placebo): entered: 40 treated: 40, analysed (for primary endpoint): 40.
Diagnosis and main criteria for inclusion:	Healthy, 18 to 60 year old male or female (post menopausal / surgically sterile females only) subjects
Test product:	BIRB 796 BS tablets
dose:	45, 60, 75, 90, 105 mg bid
mode of admin.:	per os
batch no.:	PD 2060, PD 2109 (5 mg) PD 2061 (20 mg)

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Duration of treatment:	14 days
Reference therapy:	placebo
dose:	n.a.
mode of admin.:	per os
batch no.:	PD 2059, PD 2111 (corresponding with 5mg and 20mg BIRB 796 BS)
Criteria for evaluation:	
Efficacy/PK:	Pharmacokinetics: concentration time profiles BIRB 796 BS steady state and trough levels, multiple dose pharmacokinetic parameters ($C_{max,ss}$, $AUC_{0-\tau}$, $t_{max,ss}$, $t_{1/2}$)
Safety:	Adverse events; tolerability; vital signs; routine laboratory values, EKG, physical examination
Statistical methods:	Descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy/PK results:

Following the morning dose on day 14 mean $C_{max,ss}$ values occurred at <1 hour regardless of dose group. Mean morning $C_{max,ss}$ and $AUC_{0-\tau,ss}$ ranged from 286.3 to 631.33 ng/mL, and 832.1 to 2067.53 hr·ng/mL for the five dose groups, respectively. High variability was observed between dose groups. Mean oral clearance (CL/F) value for the 105 mg dose group was much higher than other dose groups. Inter-individual variability within dose group based on morning $AUC_{0-\tau,ss}$ was lower for the three lower dose groups (CV ranging from 28% to 37%) and appeared to increase substantially for the two highest dose groups (48% for 90 mg and 80% for 105 mg). Following the evening dose, drug absorption was slightly prolonged with mean t_{max} values ranging from 1.4 to 2.5 hours. Mean evening $AUC_{0-\tau,ss}$ values were 15% to 30% higher, mean $C_{max,ss,pm}$ values were mostly lower, and mean troughs (C_{336}) were higher (ranging from 23% to 64%) than that those for the corresponding morning dose (C_{324}). Mean elimination half-life ranged from 6.7 to 8.4 hours.

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Safety results:

The overall tolerability of BIRB 796 BS was assessed as good, in the highest dose groups 12.5% (90 mg bid) and 25% (105 mg bid) of subjects were classified not satisfactory, which was mainly associated with transaminase elevation.
There were no SAEs reported in this study. The overall rate of AEs was very similar in actively treated and placebo treated subjects. The use of increasing BIRB 796 BS doses seemed to be associated with an increasing rate of subcutaneous tissue disorders, mainly dermatitis acneiform. All observed events were reversible and the vast majority were mild in intensity. Unspecific gastrointestinal AEs seemed to occur more frequently in actively treated subjects, there was however no obvious correlation with the dose administered. Treatment with BIRB 796 BS was associated with a reversible, dose dependent increase in ALT / GPT, GLDH, and, to a lesser extent, in AST / GOT. There was however no obvious correlation with the highest BIRB 796 trough concentrations or peak plasma concentrations observed during the study. The increases were not associated with signs or symptoms of liver dysfunction and were not associated with increases in bilirubin levels. There was no clinically relevant effect on other lab parameters and there was no evidence of vasculitis, pancreatic dysfunction or changes in red blood cell morphology in this study.

In the ECG analysis there were no findings of immediate clinical concern. A mild effect of BIRB 796 BS on the QT interval cannot be ruled out. The mean maximum increases in QTcF observed in all actively treated subjects was 5 to 10 msec (relative to placebo subjects). This effect was not dose dependent and there was no correlation with the actual BIRB 796 BS plasma concentration. A QTcF prolongation in this order of magnitude is considered to be of no clinical relevance.

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Conclusions:

Steady state was attained within 48 hours of multiple dose administration as indicated by the relatively constant mean morning trough concentrations. Absorption of the BIRB 796 BS tablet was relatively rapid following drug administration. However, following the evening dose, drug absorption was slightly prolonged. Morning $C_{max,ss,am}$ and $AUC_{0-\tau,ss,am}$ and evening $AUC_{0-\tau,ss,pm}$ were found to increase in a dose-proportional manner, although evening $C_{max,ss,pm}$ did not, mainly due to much higher values in the middle 75 mg dose. Variability in pharmacokinetics (PK)was relatively high between and within dose groups, especially at higher dose groups. Mean elimination half-life was relatively similar among dose groups, ranged from 6.7 to 8.4 hours. Mean oral clearance (CL/F) values were much higher for the 105 mg dose group, followed by the 60 mg dose group. No apparent relationship was found between CL/F and gender, age or body weight.

Treatment with BIRB 796 BS at doses up to 75 mg bid was safe and well tolerated, higher doses (90 and 105 mg bid) were associated with an increasing risk of transaminase elevations (primarily ALT / GPT) resulting in premature discontinuation of study treatment (as defined in the study protocol) in a few subjects in each of these dose groups. A mild QTc prolongation due to BIRB 796 BS treatment cannot be ruled out completely.

Overall, the clinical safety and pharmacokinetic data from this trial support the use of BIRB 796 BS administered in doses from 45 mg to 75 mg bid.