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***.

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:** xxx **to** xxxx		**Addendum No.:**
Report date: April 16, 2002	**Number:** U02-1303	**Study period (years):** 01-03/2001		

Title of study:	Safety and pharmacokinetics of BIRB 796 BS tablets administered twice daily orally (total daily dose 30 and 60 mg) to healthy human male subjects for 14 days. A double-blind, placebo-controlled, parallel group study.
Investigator:	[redacted]
Study center:	[redacted] Germany
Publication (reference):	not yet 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, parallel group (multiple dose level), double blinded study.
No. of subjects entered:	
total:	49
each treatment:	16 (one subject from the placebo group was withdrawn after first dose because initial exclusion criteria determined to be violated. This subject was replaced)
Diagnosis and main criteria for inclusion:	healthy male subjects, age 18 to 45
Test product:	BIRB 796 BS tablets: 5 mg, 20 mg
dose:	15 mg (3 x 5 mg) bid, 30 mg (2 x 5 mg + 1 x 20 mg) bid for 14 days
mode of admin.:	*per os*
batch no.:	PD-1961 (5 mg), PD-1962 (20 mg)
Duration of treatment:	14 days
Reference therapy:	placebo tablets
dose:	3 placebo tablets bid for 14 days
mode of admin.:	*per os*
batch no.:	PD-1965
Criteria for evaluation:	
Efficacy / Pharmacokinetics:	no efficacy endpoints plasma concentration-time profiles of BIRB 796 BS, pharmacokinetic parameters

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product:		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** xxx **to** xxxx		**Addendum No.:**
Report date: April 16, 2002	**Number:** U02-1303	**Study period (years):** 01-03 / 2001		

Safety:	adverse events, tolerability, vital signs, routine laboratory values, EKG, physical examination
Statistical methods:	descriptive statistics

SUMMARY - CONCLUSIONS:

Efficacy results: not applicable

Pharmacokinetic results: After administration of the first tablet dose of BIRB 796 BS on day 1, there was rapid absorption with a mean t_{max} of 1.03 and 0.81 hr for the 15 and 30 mg dose groups, respectively. Mean ± SD C_{max} values were 81.0 ± 30.2 and 152.2 ± 61.3 ng/mL, and AUC_{0-12} values were 234.0 ± 74.9 and 416.6 ± 205.2 hr·ng/mL, respectively. On day 14, after the morning dose, mean $C_{max,ss}$, $AUC_{0-\tau,ss}$ and trough (C_{324}) were 109 ± 51 ng/mL, 334 ± 145 ng·hr/mL and 8.4 ± 5.7 ng/mL (15 mg); and 208 ± 109 ng/mL, 659 ± 449 ng·hr/mL and 17.5 ± 19.7 ng/mL (30 mg), respectively; whereas after the evening dose, mean $C_{max,ss}$, $AUC_{0-\tau,ss}$, and trough (C_{336}) were 86 ± 35 ng/mL, 401 ± 166 ng·hr /mL and 11.0 ± 7.6 ng/mL (15 mg), and 162 ± 76 ng/mL, 782 ± 483 ng·hr/mL and 23.4 ± 24.9 ng/mL (30 mg), respectively. Drug absorption after the evening dose was slightly prolonged with a t_{max} mostly observed at 1.5 to 2 hours, resulting in a slightly (about 20%) lower $C_{max,ss}$, higher trough and $AUC_{0-\tau,ss}$. Mean $t_{1/2}$ was 7.4 ± 2.0 hr and 7.3 ± 1.4 hr, respectively.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product:		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** xxx **to** xxxx		**Addendum No.:**
Report date: April 16, 2002	**Number:** U02-1303	**Study period (years):** 01-03 / 2001		

Safety results:

BIRB 796 BS and placebo were well tolerated at doses up to 30 mg twice a day for 2 weeks. Eight subjects, equally distributed amongst the treatment groups had adverse events. However, there were no adverse events related to the study medication. Two subjects did not receive their full course of drug treatment, both for adverse events unrelated to the treatment (one in the placebo group and one in the 15 mg bid group).

Previous studies have found an increase in liver transaminases, especially at single daily doses of 150 mg for one week [U01-1537]. Although sporadic elevations in ALT were seen in the current study, the pattern was not consistent with that seen with 150 mg daily for one week. In that study (1175.3), ALT values were elevated within several days of starting drug administration and peaked several days after a full 7 days of drug administration, with eventual resolution over the following weeks. In the current study, the elevations sometimes occurred early and sometimes late in treatment. Several subjects on active treatment had a return of their values to the normal range, even while continuing therapy. Others had ALT values that returned to normal within one to two days of stopping drug. In some subjects the increases were transient. As well, two of the subjects with an increase in ALT above the normal range were in the placebo group. In addition, the pattern was not consistent between subjects within dose groups and there was no dose relationship between the elevations and the drug administered. Also, one subject in the 30 mg bid dose group had elevation in ALT even prior to drug administration. The changes in ALT in this study may reflect the natural variability seen in institutionalised subjects. Unlike study 1175.3, no relation was found between peak serum drug levels and peak elevation in ALT in the current study.

As opposed to the two previous studies with single doses up to 600 mg (1175.1) and multiple doses up to 150 mg [U00-1627, U01-1537], there was also no elevation in γ-GT. In study 1175.1 there was an elevation in total bilirubin attributed to the vehicle used in the study, polyethylene glycol 400. Although there were sporadic elevations in total bilirubin in the current study, as would be expected with the absence of PEG 400, total bilirubin was not consistently increased.

In concordance with clinical studies performed to date, there were no clinical or laboratory signs of vasculitis or pancreatic dysfunction. Although red cell morphology changes have been seen in preclinical studies, no change sin the occurrence of poikilocytosis or schistocytosis were detected, even with intensive daily monitoring of red cell smears. Laboratory analysis did not demonstrate significant differences related to the BIRB 796 BS and placebo groups. As in previous phase I studies, EKG findings did not reveal any treatment influence or suggestion of prolongation of QT interval.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product:		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** xxx **to** xxxx		**Addendum No.:**
Report date: April 16, 2002	**Number:** U02-1303	**Study period (years):** 01-03 / 2001		

Conclusions:

Plasma BIRB 796 BS concentrations were on average higher on day 14 than day 1. Morning trough concentrations were relatively constant after 24 hr, suggesting steady-state had been attained thereafter. Following twice daily dosing, a lower mean fluctuation ratio (16) was observed between steady state peak and trough concentrations compared to once daily dosing (≥28) [U01-1537]. Drug absorption after the evening dose was slightly prolonged with a t_{max} mostly observed at 1.5 to 2 hours, resulting in a slightly (about 20%) lower $C_{max,ss}$, higher trough and $AUC_{0-\tau,ss}$. Steady state mean $C_{max,ss}$ $AUC_{0-\tau,ss}$ and trough were dose proportional. Based on the $AUC_{0-\tau,ss,}$ interindividual variability was moderately high, with a coefficient of variation of 43% and 68% for the respective dose groups.

A clinical correlate to preclinical concerns regarding potential increase in QT interval, vasculitis and abnormal red blood cell morphology (schistocytosis and acanthocytosis) and pancreatic dysfunction have not been found in the current study. The low-grade elevations in hepatic transaminases seen at higher doses in previous studies have not been found at the current dose levels. BIRB 796 BS is well tolerated at doses up to 30 mg bid for two weeks.