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:**		**Addendum No.:**
Report date: 06 JUN 2003	**Number:** U03-1389	**Study period (years):** 2001 - 2002		

Title of study:	A randomised, parallel, double-blind, placebo-controlled study to investigate efficacy and safety of different doses (5, 10, 20 and 30 mg) of BIRB 796 BS administered twice a day orally over 4 weeks in patients with active Rheumatoid Arthritis who have failed at least one DMARD		
Investigator:	Rheumatologists		
Study centers:	Multi-national, multi-centre		
Publication (reference):	N.A.		
Clinical phase:	IIa		
Objectives:	The objective was to determine the effects of BIRB 796 BS on CRP and clinical parameters in Rheumatoid Arthritis as measures of efficacy, and on population pharmacokinetics and safety parameters		
Methodology:	Randomised, double-blind, placebo-controlled, dose-response, multi-centre, parallel		
No. of subjects:			
planned:	Total	enrolled: 180	entered: 150
actual:	Total	enrolled: 253	entered: 167
	Placebo		entered: 33
	BIRB 796 5 mg bid		entered: 32
	BIRB 796 10 mg bid		entered: 37
	BIRB 796 20 mg bid		entered: 33
	BIRB 796 30 mg bid		entered: 32
Diagnosis and main criteria for inclusion:	Active RA, functional class I-III, men or women aged 18-75 years, failure of at least one DMARD, CRP ≥ 2.0 mg/dl		
Test product:	BIRB 796 BS		
dose:	Twice daily doses of 5, 10, 20 or 30 mg, respectively		
mode of admin.:	oral		
batch no.:	5 mg PD-2060, 20 mg PD-2061		
Duration of treatment:	4 weeks		
Reference therapy:	Placebo tablets matching 5, 10, 20 or 30 mg		
dose:	N.A.		
mode of admin.:	oral		
batch no.:	PD 2059		

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Criteria for evaluation:

Efficacy: CRP, swollen and tender joint counts, patients assessment of disease activity and pain, physicians assessment of disease activity, ESR, ACR 20/50/70, HAQ, TNF-α, sTNF-R, IL-1ra, IL-6, MMP-3, VEGF, number of drop-outs due to lack of efficacy

Safety: Adverse events, laboratory evaluations, ECGs, body temperature, physical exams, number of withdrawals due to lack of efficacy

Statistical methods: ANOVA, ANCOVA, t-test, Fishers Exact Test, Wilcoxon Rank Sum Test, Chi-square Test

SUMMARY – CONCLUSIONS:

Efficacy results:

There was a dose-dependent decrease in the primary endpoint for the BIRB 796 BS treatment groups compared to placebo. This difference failed to achieve statistical significance. The reduction in CRP was greatest in the first two weeks of treatment.

Among the secondary endpoints, ESR also showed a dose-dependent decrease and was closest to a statistically significant difference over placebo for the BIRB 30 mg group.

There was no statistically significant difference of any BIRB 796 BS treatment group compared to placebo for ACR 20 or DAS 28.

There was a clear dose-dependent decrease in the number of drop outs due to lack of efficacy.

The concentrations obtained at pre-dose and one hour post-dose at week 4 increased proportionately with increasing dose. Inter-individual variability was high with a coefficient of variation of at least 70% based on both concentration values. Compared the time points at week 4 in RA patients to normal subjects observed at the same 30 mg bid dose in trial 1175.14 (U02-1303), the one-hour concentration in RA patients was 1.2-fold higher than normal subjects based on geometric mean, while the trough concentration was 2.9-fold higher. Note that a majority of RA patients were female in this trial, while normal subjects were all or mostly males. However, there appears to be no consistent relationship between gender and plasma drug concentrations. No apparent correlations were observed between these plasma concentrations and age and body weight based on dose normalized data.

There were no apparent trends in the data that may suggest a correlation between these pharmacodynamic endpoints (CRP, ESR and IL-6) and BIRB 796 BS plasma concentrations.

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Safety results:	BIRB 796 BS in doses up to 30 mg bid has been generally well tolerated. The overall frequency of mild AEs appeared to be higher in BIRB 796 BS treated patients compared to placebo. In the absence of a clear dose relationship, gastrointestinal and skin AEs showed a potential trend. On the level of individual AEs there was no difference between BIRB 796 BS and placebo. Treatment discontinuation due to worsening of disease as AE was most frequently observed on placebo treatment. None of the previously identified pre-clinical potential safety liabilities of BIRB 796 BS (e.g. dog systemic vasculitis, RBC morphology abnormalities in monkey, and pancreas acinar apoptosis in rat) were observed, based on laboratory evaluations including RBC morphology changes, coagulation parameters, increases in white blood cell counts and assessments of pancreatic function (amylase, lipase and glucose). The LFT results showed no difference from placebo patients. The ECG evaluation did not rule out an effect of BIRB 796 BS on cardiac repolarization but there was no evidence of any effect on heart rate, cardiac conduction or ECG morphology. The small effect of BIRB 796 BS on cardiac repolarization of <5 msec should be viewed with caution since the study was not designed to detect small changes in QT interval durations.

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Conclusions:

The trial failed to show significance for the primary endpoint CRP after four weeks of treatment. There was a dose-dependent trend to decrease CRP. More recent data on the effect of anti-TNF treatment on CRP in RA that had not been available during the planning period of this trial suggests that this trial may have been underpowered.

The effect size on CRP at four weeks of BIRB 796 BS given in doses up to 30 mg bid compares with the effect seen in a low dose subtherapeutic (10 mg s.c. twice weekly) trial of etanercept at three months.

The fact that the maximal effect on CRP was observed for all treatment groups earlier than at four weeks might be due a bias of the DMARD washout and the placebo effect and should not lead to the conclusion that there is only a temporary effect. Further studies applying higher doses over longer periods of time are required to study this phenomenon.

In contrast to parenteral anti-TNF-agents, BIRB 796 BS in doses up to 30 mg could not demonstrate a difference to placebo on composite scores of clinical efficacy or single clinical efficacy parameters within four weeks. This is not unusual for standard oral DMARD therapies, where (1) an effect on CRP is observed before the onset of clinical improvement and (2) the onset of clinical improvement occurs beyond week 4.

BIRB 796 BS taken in doses up to 30 mg bid was safe and generally well tolerated. Systemic drug exposure was dose-proportional. Peak (one-hour) concentration in RA patients was slightly higher than in normal subjects at the same 30 mg bid dose although the trough concentration was much higher. No correlation was found between plasma concentration and demographic factors such as gender, age, or body weight. Relationship between plasma concentrations at week 4 and pharmacodynamic endpoints (CRP, ESR and IL-6) was not found.

In the absence of a target organ of toxicity, the upper limit of the safety window for BIRB 796 BS treatment could not be identified in RA patients. No new or unexpected risks of treatment with BIRB 796 BS are apparent from this trial.

The efficacy and safety data from this trial support the need for a subsequent trial of BIRB 796 BS at higher doses and longer duration to evaluate the therapeutic potential of this compound in RA.