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***.

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Report date: 27 OCTOBER 2004	**Number:** U04-1940	**Study period (dates):** 18 Oct 2001 – 15 Jan 2004 (last follow-up visit)		

Title of study:	A randomised, double-blind, placebo-controlled, five* parallel groups, dose finding study of BIRB 796 BS (10, 20, 30, and 60 mg*) administered twice a day orally over 8 weeks in patients with moderate to severe Crohn's disease followed by a 18 weeks treatment extension in patients with clinical remission or clinical response after 8 weeks treatment with the respective dose of BIRB 796 BS - extension phase. * subsequent to amendment 4 (dated 11 Jun 2002) a 60 mg b.i.d. group was included.
Investigator:	[redacted]
Study centre(s):	Multicentre Study, 54 study centres, cf. Appendix 16.1.4
Publication (reference):	Data of this study has not been published.
Clinical phase:	IIa
Objectives:	The primary objective of this extension study was to obtain long-term safety data for BIRB 796 BS in patients with moderate to severe Crohn's disease after 26 weeks of treatment. Secondary objectives were the evaluation of efficacy of BIRB 796 BS to induce clinical remission and response over 26 weeks of treatment.
Methodology:	Randomised, double-blind, placebo-controlled, multicentre, 5 parallel groups
No. of subjects: **planned (for main phase):**	224 patients, 50 for the placebo, 10 mg b.i.d., 20 mg b.i.d., 30 mg b.i.d. groups, and 24 in the 60 mg b.i.d. group (subsequent to amendment 4).
actual:	enrolled: 354 entered main phase: 284 entered extension phase: 130 Placebo: entered: 31 treated: 31 analysed: 31 10 mg b.i.d.: entered: 26 treated: 26 analysed: 26 20 mg b.i.d.: entered: 30 treated: 30 analysed: 30 30 mg b.i.d.: entered: 26 treated: 26 analysed: 26 60 mg b.i.d.: entered: 17 treated: 17 analysed: 17

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Diagnosis and main criteria for inclusion:	
Main phase:	Male and female patients 18 -65 years of age with moderate to severe Crohn's disease (CDAI ≥220 to ≤450, at baseline) with a diagnosis of Crohn's disease for at least 6 months and on stable concomitant therapy of immunosuppressants, steroids, budesonide, 5-ASA-drugs, 6-mercaptopurine, azathioprine, or methotrexate.
Extension phase:	Clinical remission (CDAI <150) or clinical response (reduction of CDAI≥70) at week 8.
Test product:	BIRB 796 BS
dose:	Twice daily (b.i.d.) doses of 10, 20, 30, or 60 mg
mode of admin.:	Oral
batch no.:	PD-2086 (5 mg tablets), PD-2087 (20 mg tablets)
Duration of treatment:	8 + 18 weeks. Patients with clinical remission or clinical response at week 8 were offered to enter an extension phase of 18 weeks treatment. Data of main phase were reported in a separate document.
Reference therapy:	Placebo tablets
dose:	Twice daily (b.i.d.)
mode of admin.:	Oral
batch no.:	PD-2085
Criteria for evaluation:	
Efficacy:	CDAI, IBDQ, fistulae reduction, CRP concentration, daily corticosteroid dose after week 10, number of withdrawals due to treatment failure
Safety:	Adverse events, safety laboratory parameters, haematology, coagulation parameters, serum chemistry, ECG, urinalysis, and vital signs
Statistical methods:	descriptive statistical methods
SUMMARY – CONCLUSIONS:	
Efficacy results:	This study of 10 mg b.i.d., 20 mg b.i.d, 30 mg b.i.d., and 60 mg b.i.d. BIRB 796 BS did not show any effect on clinical remission, clinical response, disease-specific quality of life, or change in CRP-level over 26 weeks compared with placebo.

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Safety results:	Overall BIRB 796 BS in doses of up to 60 mg b.i.d. was well tolerated compared with placebo over a treatment period of 26 weeks. With respect to the adverse events profile no conclusive difference between the placebo group and the BIRB 796 BS dose groups was apparent. There were no safety concerns with respect to haematology, red blood cell morphology, or coagulation indices. Renal function and metabolic parameters were generally not impaired in the BIRB 796 BS dose groups compared with the placebo group. With regard to liver function, there was a tendency towards more and higher transaminase (ALT, AST) elevations in the BIRB 796 BS dose groups than in the placebo group although a clear dose-relationship was not observed. The analysis of ECG-data showed a small but clear dose-dependent effect on QT-prolongation at week 2, but not at week 8: doses up to 20 mg b.i.d. did not impact on QT time while the higher BIRB 796 BS doses led to a mean change from baseline of QTcF of 5.79 msec (30 mg b.i.d.) and 9.65 msec (60 mg b.i.d.). At week 26, a prolongation of QTcB was noticed in the 30 mg b.i.d. (14.92 msec) and the 60 mg b.i.d. dose groups (8.60 msec), and a prolongation of QTcF was observed only in the 30 mg b.i.d. dose group (9.62 msec).
Conclusions:	Studies with BIRB 796 BS were terminated on 19 Nov 2003 due to safety concerns. Generally and overall, the treatment with BIRB 796 BS was well tolerated over a period of 26 weeks. The overall rates of adverse events were similar between the BIRB 796 BS dose groups and the placebo group. No clear difference between the treatment groups could be observed for adverse events of severe intensity. The highest incidence of drug-related adverse events occurred in the 30 mg b.i.d. dose group (38.5%); the placebo rate was 19.4%. The highest incidence of serious adverse events was reported in the 20 mg b.i.d. BIRB 796 BS dose group (20.0%); the placebo rate was 3.2%. Elevations of liver enzymes (ALT, AST) were more severe and more frequent in the BIRB 796 BS dose groups than in the placebo group. However, no clear dose-dependency was observed. Also, there was a small clinically not significant dose-dependent prolongation of the QT-interval in the 30 mg b.i.d. and 60 mg b.i.d. BIRB 796 BS dose groups at week 2 that was not noticed at week 8. At week 26, the mean QTcF and QTcB prolongations were substantially higher in the 30 mg b.i.d. and 60 mg b.i.d. dose groups than in the placebo group. None of the BIRB 796 BS dose groups showed any effect with respect to clinical remission in comparison with placebo. Also, there was no effect of any BIRB 796 dose group with regard to clinical response, change in IBDQ, or reduction in the number of draining fistulae. Furthermore, for C-reactive protein levels there was no difference between any of the BIRB 796 BS dose groups and the placebo group during the extension study phase. Thus, similar to the main study, the extension study failed its efficacy objectives.