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: 24 JUN 2004	**Number:** U04-1409	**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. * 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 study was to establish the efficacy of BIRB 796 BS to induce remission in patients with moderate to severe Crohn's disease after 8 weeks of treatment. Secondary objectives were the evaluation of safety, tolerability, and pharmacokinetics of BIRB 796 BS over 8 weeks of treatment.
Methodology:	Randomised, double-blind, placebo-controlled, multicentre, 5 parallel groups
No. of subjects: **planned:**	224 patients, 50 for the placebo, 10 mg b.i.d., 20 mg b.i.d., 30 mg b.i.d., and 24 in the 60 mg b.i.d. group (subsequent to amendment 4).
actual:	enrolled: 354 entered: 284 Placebo: entered: 62 treated: 62 analysed*: 62 10 mg b.i.d. entered: 64 treated: 64 analysed*: 64 20 mg b.i.d. entered: 61 treated: 61 analysed*: 61 30 mg b.i.d. entered: 65 treated: 65 analysed*: 65 60 mg b.i.d. entered: 32 treated: 32 analysed*: 31 * (for primary endpoint)

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Diagnosis and main criteria for inclusion:	Male and female patients 18 -65 years of age with moderate to severe Crohn's disease (CDAI ≥220 to ≤450, at baseline) with a diagnose 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.
Test product: **dose:** **mode of admin.:** **batch no.:**	BIRB 796 BS Twice daily (b.i.d) doses of 10, 20, 30, or 60 mg Oral PD-2086 (5 mg tablets), PD-2087 (20 mg tablets)
Duration of treatment:	8 weeks. Patients with clinical remission and clinical response at week 8 were offered to enter an extension phase of 18 weeks treatment. Data of extension phase will be reported in a separate document.
Reference therapy: **dose:** **mode of admin.:** **batch no.:**	Placebo tablets Twice daily (b.i.d) Oral PD-2085
Criteria for evaluation: **Efficacy:** **Safety:**	 CDAI, IBDQ, fistulas reduction, CRP concentration, number of withdrawals due to treatment failure, CDEIS and histological scoring of biopsies (substudy) Criteria for Pharmacokinetics: Drug plasma concentration measurements Adverse events, safety laboratory parameters, haematology, coagulation parameters, serum chemistry, ECG, urinalysis, and vital signs
Statistical methods:	Exact conditional test for stratified 2x2 contingency tables for primary efficacy analysis; otherwise descriptive statistical methods; population pharmacokinetics methods.

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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 at week 8 compared with placebo.
Pharmacokinetic results:	Both trough and 1-hour BIRB 796 BS concentrations in Crohn's disease patients collected at week 8 were shown to be variable, but roughly increased proportionately with dose up to the 30 mg b.i.d. The 60 mg b.i.d. dose group exhibited similar trough but slightly lower 1-hour post-dose concentrations compared with the 30 mg b.i.d. dose group.
Safety results:	Overall BIRB 796 BS in doses of up to 60 mg b.i.d. was well tolerated compared with placebo. However, in respect to adverse events with severe intensity and serious adverse events, the BIRB 796 BS dose groups exhibited higher incidences than the placebo group. There were no safety concerns in respect to haematology, red blood cell morphology, or coagulation indices, also renal function and metabolic parameters were generally not impaired in the BIRB 796 BS dose groups compared with the placebo group. In respect 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 effect on QT-prolongation. Doses up to 20 mg b.i.d. did not impact on QTcB or QTcF time. For the 30 mg b.i.d. group and the 60 mb b.i.d. group the mean changes from baseline in QTcF were 3.18 msec and 5.47 msec, respectively.

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Conclusions:	The study was terminated on 19 Nov 2003 due to safety concerns. None of the BIRB 796 BS dose groups showed any effect in respect to clinical remission in comparison with placebo. Also, there was no effect of any BIRB 796 dose group in respect 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 at study end. Thus the study failed its efficacy objectives entirely. Generally, the treatment with BIRB 796 BS was well tolerated. There were no deaths. Serious adverse events were infrequent; the most common SAEs were gastrointestinal disorders indicating a worsening or complications of Crohn's disease. The overall rates of adverse events were similar between the BIRB 796 BS dose groups and the placebo group. However, there was a tendency towards a higher frequency of adverse events with a severe intensity in the BIRB 796 BS groups. Elevations of liver function tests (primarily ALT and AST) were higher and more frequent in the BIRB 796 BS dose groups than in the placebo group. However, no close relationship to the BIRB 796 BS dose could be established. Also, there was a small mean QT-prolongation of 3-6 msec in the two highest BIRB 796 BS dose groups.