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**		
Name of finished product: BIRB 796 BS				
Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 17 June 2003	**Number:** U03-3137-01	**Study period (dates):** 27 June 2001 - 17 September 2002		**Revision date:** 09 December 2004

Title of study:	Phase II, randomized, double-blind, placebo controlled, multi-center, four week trial of BIRB 796 BS 5, 10, 20 and 30 mg oral tablets versus placebo administered BID in patients with moderate to severe plaque-type Psoriasis
Investigator:	Multi-center study without official designation of a Principal or Coordinating Investigator
Study centers:	Multi-center study, cf. Appendix 16.1.4
Publication (reference):	Data from this study have not been published to date
Clinical phase:	IIa
Objectives:	The clinical objective of this study was to determine the effect of BIRB 796 BS on pharmacodynamic markers of psoriasis as a measure of efficacy, to determine the population pharmacokinetics of BIRB 796 BS and to determine the safety of BIRB 796 BS over 4 weeks of treatment in patients with moderate to severe plaque-type psoriasis.
Methodology:	This was a multi-center, double-blind, double-dummy, placebo-controlled, four-week trial in patients with moderate to severe psoriasis.
No. of subjects:	
planned:	entered: 150
actual:	enrolled: 367 entered: 182 placebo entered: 37 treated: 37 analysed (for primary endpoint): 37 BIRB 796 BS 5 mg entered: 36 treated: 36 analysed (for primary endpoint): 34 BIRB 796 BS 10 mg entered: 36 treated: 36 analysed (for primary endpoint): 35 BIRB 796 BS 20 mg entered: 36 treated: 36 analysed (for primary endpoint): 34 BIRB 796 BS 30 mg entered: 37 treated: 37 analysed (for primary endpoint): 34
Diagnosis and main criteria for inclusion:	Patients with moderate to severe plaque-type psoriasis with ≥5% body surface area involvement

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Test product:	BIRB 796 BS
dose:	5, 10, 20 and 30 mg BID
mode of admin.:	oral
batch no.:	PD-2042, PD-2001
Duration of treatment:	4 weeks
Reference therapy:	placebo tablets
dose:	N/A
mode of admin.:	oral
batch no.:	PD-1997
Criteria for evaluation:	Patients with moderate to severe plaque-type psoriasis with ≥5% body surface area involvement.
Efficacy:	Final primary efficacy variables were the percent changes from baseline in PASI score and pathological thickness, and a qualitative measure of K16 positive keratinocytes from the skin biopsy samples. Final secondary efficacy variables were: other assessments of the PASI score, target lesion assessment, number of epidermal and dermal T-cells (biopsy), a qualitative measure of ICAM-1 (biopsy), quantitative RT-PCR gene expression for cytokines (K16 mRNA, IL8 mRNA, iNOS, TNFα, IFN gamma, and HARP), immunological serum markers of disease activity (sIL2R, TNF-α, sTNR-R, VEGF, e-Selectin and sICAM-1) and further analyses of the primary variables. Estimation of population pharmacokinetic parameters of BIRB 796 BS was based on random plasma samples.
Safety:	The primary measures of safety will be adverse event reporting, laboratory assessments, ECGs, vital signs and physical exam.
Statistical methods:	The method of analysis of the quantitative endpoints (total PASI score, pathological thickness, and number of epidermal and dermal T-cells) was the Wilcoxon Rank-Sum test, stratified by center. Qualitative measures of ICAM-1 and K16 positive keratinocytes and other quantitative measures were analyzed using the Cochran-Mantel-Haenszel test, stratified by center. Each dose of BIRB 796 BS was compared separately to placebo, using the Bonferoni-Holm procedure for multiple comparisons on the primary analyses.

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SUMMARY – CONCLUSIONS:

Efficacy results: BIRB 796 BS showed a dose dependent decrease in pathological thickness. At Week 4, a 31% median reduction was observed in the 30 mg BIRB 796 BS treatment group compared to a 5% median reduction in placebo (p=0.0089). Secondary histopathhological endpoints (pathological thickness 20% responder and histopathologist's global assessment) were statistically significant for 20 mg and 30 mg over placebo at Week 4. No evidence of clinical efficacy was evident at 4 weeks. RT-PCR endpoints showed numerical advantages for 30 mg over placebo.

Safety results: BIRB 796 BS was safe and well tolerated in all dose groups. There was no difference in the incidence of adverse events across treatment groups and compared to placebo. No serious adverse events were reported on treatment and only five (3%) patients discontinued due to adverse events. There were no clinically significant effects on laboratory values, although there were mild, transient increases in transaminases observed. There was no effect on heart rate, cardiac conduction or ECG morphology. There was a small, clinically non-significant effect of BIRB 796 BS on cardiac repolarization, but the limitations of the trial design make this result inconclusive.

Pharmacokinetics BIRB 796 BS Concentration-time data collected at three visits showed that they were randomly distributed well over the 12-hour dosing interval for each dose group. Both trough and one-hour concentrations of BIRB 796 BS at Week 4 (Visit 8) increased with dose.

Conclusions: BIRB 796 BS was safe and well tolerated at doses up to 30 mg BID. The efficacy data suggest BIRB 796 BS has a beneficial effect on the pathophysiology of psoriasis at the tissue level as evidenced by improvement in the underlying histopathology. Further study with doses of BIRB 796 BS 30 mg or higher, and a longer duration of exposure (≥12 weeks) are indicated to establish a clinical benefit to patients.