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***.

2. SYNOPSIS

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:** to		**Addendum No.:**
Report date: 8 March 2001	**Number:** 1175.4	**Study period (years):** 2-4/2000		

Title of study:	The effect of single oral dose BIRB 796 BS (50 and 600 mg) on endotoxin-induced inflammatory responses in healthy human subjects. A placebo-controlled, randomised, parallel, double-blinded study.
Investigator:	[redacted]
Study centre:	[redacted] The Netherlands
Publication (reference):	not as yet published
Clinical phase:	I
Objectives:	To determine the effect of a single dose BIRB 796 BS on systemic inflammatory responses induced by endotoxin in healthy humans
Methodology:	Single dose (2 dose levels total), randomised, placebo controlled, parallel double blinded
No. of subjects entered:	
total:	24
each treatment:	8 at 50 mg BIRB 796 BS, 8 at 600 mg BIRB 796 BS, 8 at placebo
Diagnosis and main criteria for inclusion:	healthy male subjects, age 18 to 35 years
Test product:	BIRB 796 BS in polyethylene glycol 400 (PEG 400) solution
dose:	50 mg, 600 mg
mode of admin.:	*per os*
batch no.:	BIRB 796 BS: PD-1973, PD-1975, PD-1976; PEG 400: PD-1977
Duration of treatment:	single dose
Reference therapy:	PEG 400
dose:	15 ml
mode of admin.:	*per os*
batch no.:	PD-1977

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Criteria for evaluation:	
Efficacy / Pharmacokinetics:	Primary endpoints: pharmacodynamics (tumour necrosis factor alpha concentrations (TNFα)) Secondary endpoints: pharmacokinetics: plasma concentration-time profile BIRB 796 BS pharmacodynamics: pro-inflammatory cytokines, anti-inflammatory cytokines and inhibitors, endothelial cell activation markers, acute phase proteins, *ex vivo* p38 mitogen activated protein kinase (MAPK) phosphorylation, flow cytometry cell surface markers, leukocyte response, clinical pharmacodynamic endpoints
Safety:	Adverse events; tolerability; vital signs; routine laboratory values
Statistical methods:	descriptive statistics

SUMMARY - CONCLUSIONS:

Efficacy results:

BIRB 796 BS administered orally 3 hours prior to lipopolysaccharide (LPS) challenge inhibited LPS induced TNFα production by 88% and 97% at 50 and 600 mg respectively. BIRB 796 BS also inhibited pro-inflammatory cytokines (interleukin (IL)-6, IL-8, IL-1r), CRP, and neutrophil activation (elastase, elastase-α1-antitrypsin and Mac-1/L selectin ratio) were also inhibited. This data was in accordance with the model of LPS-induced TNFα production in Cynomolgus monkeys [U98-3153]. The E_{max} model described the relationship between the percent inhibition and the pre-challenge plasma BIRB 796 BS concentration.

Since BIRB 796 inhibited the activation of the inflammatory cascade induced by exposure to LPS, amelioration of clinical effects was also expected. This was seen in relation to gastrointestinal signs and symptoms (nausea, vomiting and abdominal pain), chills, fever, myalgia, headache, and backache. There appeared to be a dose effect relationship with lower incidence and severity of signs or symptoms as a whole with increasing dose of BIRB 796 BS.

Pharmacokinetics

Mean ± SD peak concentrations (C_{max}) were 390.4 ± 129.7 and 3896 ± 867 ng/mL for the 50 and 600 mg dose groups respectively, and mean ± SD $AUC_{0-\infty}$ values were 1109.6 ±242.6 and 23507 ±8624.5 ng • hr/mL for the respective doses. Mean t_{max} values were slightly longer in the 600 mg dose group, with a mean t_{max} of 1.19 hours, versus 0.75 hours as observed for the 50 mg dose group. A mean elimination half-life of approximately 5.2 and 9.8 hours and a mean apparent oral clearance of 47 and 29 L/hr was observed for the 50 and 600 mg dose groups.

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Safety results:	BIRB 796 BS was well tolerated. There were no adverse events in the 600 mg group. One subject receiving 50 mg BIRB 796 had a mild headache. The placebo group had seven adverse events. Most adverse events (e.g. flu-like symptoms such as headache) could be attributed to the known effects of endotoxin administration rather than BIRB 796 BS. Nausea, vomiting, myalgia, headache, and backache occurred in all treatment groups, but was lower with BIRB 796 BS treatment in comparison to placebo. Vital signs were altered with endotoxin administration as has been previously reported in other studies using the LPS induced cytokine model. BIRB 796 BS was associated with a decrease in these LPS effects in regards to oral body temperature and pulse rate. An endotoxin-associated increase in white blood cell count and neutrophils was decreased with BIRB 796 BS administration. As in previous BIRB 796 BS studies, there were small reversible increases in total bilirubin likely associated with the 15 ml PEG 400 vehicle, and a small rise in γ-GT with 600 mg BIRB 796 BS. No other alterations in liver transaminases were detected. The overall tolerability was better in the group receiving BIRB 796 BS than placebo, likely related to a decrease in LPS related adverse effects.
Conclusions:	BIRB 796 BS potently inhibits TNFα production in an LPS induced TNFα model and is associated with lower incidence and severity of LPS related clinical signs and symptoms. Following oral administration of BIRB 796 BS in a PEG 400 solution, absorption was rapid. Mean peak concentrations (C_{max}) occurred approximately within an hour after administration, and appeared to occur slightly later in the higher dose group. A distribution phase was observed after t_{max}, followed by a slower elimination phase with a mean half life of approximate 5-9 hours. C_{max} appeared to be dose proportional, while super-dose-proportionality was observed for $AUC_{0-\infty}$. BIRB 796 BS at a dose up to 600 mg in 15 ml PEG 400 was well tolerated. γ-GT should be monitored when such high doses are administered in future studies. Total bilirubin should be monitored if PEG 400 is administered at doses of 15 ml.