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:				
Name of active ingredient: BIRB 796 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 10 October 2003	**Number:** U03-3274-01	**Study period (dates):** 24 October 2002 - 16 November 2002		

Title of study:	A phase I single oral dose (100 mg) trial to characterize the excretion balance of ^{14}c-radiolabeled BIRB 796 BS and to determine its metabolites in normal male subjects
Investigator:	[redacted]
Study center(s):	[redacted]
Publication (reference):	
Clinical phase:	I
Objectives:	To characterize the pharmacokinetics of ^{14}C-radiolabeled BIRB 796 BS and its metabolites including excretion and mass balance of parent compound and radioactivity; to isolate, identify and quantify major radiolabeled metabolites of BIRB 796 in plasma, urine and feces
Methodology:	Open-label trial: a single dose of a PEG 400 solution containing 100 mg of unlabeled BIRB 796 BS and approximately 98 µCi of ^{14}C-radiolabeled BIRB 796 BS were administered to six normal male subjects.
No. of subjects entered:	6
Diagnosis and main criteria for inclusion:	Healthy male subjects, age 18 to 45 years
Test product:	^{14}C-BIRB 796 BS in polyethylene glycol (PEG) 400 solution
dose:	100 mg, approximately 98 µCi
mode of admin.:	P.O.
batch no.:	Unlabeled BIRB 796 BS: PD 2206 ^{14}C-radiolabeled BIRB 796 BS: BL-5664-121 PEG 400: PD 2207
Duration of treatment:	single dose
Reference therapy:	N/A

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Criteria for evaluation:

Efficacy: There were no efficacy endpoints.

Pharmacokinetics:

- Primary endpoints:
  Cumulative amount of ^{14}C-radioactivity excreted in feces and urine; C_{max}, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$ of ^{14}C-BIRB 796 BS-derived radioactivity in plasma and blood and BIRB 796 BS in plasma, erythrocyte-plasma partition ratio of ^{14}C-radioactivity; isolation, identification and quantification of radiolabeled metabolites in urine, feces and plasma
- Secondary endpoints:
  Evaluation of excretion of ^{14}C-radioactivity in saliva and expired air

Safety: Adverse event reporting, physical exam, vital signs, ECG and laboratory assessments.

Statistical methods: Descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy results: Not applicable

Pharmacokinetic results: A mean of 79.4% of dose was excreted in the feces, and 3.55% of dose was excreted in the urine through 264 hours postdose. Radioactivity in expired air and saliva was low, with mean recoveries of 0.58 and 0.02% of the administered dose, respectively. The mean total recovery of radioactivity was 83.7% of dose with total recovery in individual subjects ranging from 60.2 to 92.1% of dose. The time course of ^{14}C-radioactivity concentrations in blood and plasma were similar although blood showed higher peak and declined faster. Mean $t_{1/2}$ and mean residence time (MRT) in plasma was 104.2 hr and 149.1 hr, respectively, both of which were approximately 1.5-fold longer than blood. Mean $AUC_{0-\infty}$ in plasma was two-fold higher than blood, corresponding about a 2-fold lower in apparent oral clearance. Total radioactivity was taken up into red blood cells initially, but over time it declined to essentially no uptake.

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Safety results:	Six healthy male volunteers received a single dose of 100 mg ^{14}C-radiolabeled BIRB 796 BS (approximately 98µCi). The dose was well-tolerated by all subjects. Three post-treatment adverse events considered mild in nature, were experienced by one subject only. Two subjects had mildly elevated liver function tests after taking the study drug, which were not clinically significant. These results are consistent with the safety conclusions from Trial 1175.1 in which single doses up to 600 mg BIRB 796 BS were well-tolerated in healthy male subjects [U00-1627]. In Trial 1175.1 there were no clinically significant adverse events, laboratory changes or dose-dependent adverse events associated with the use of BIRB 796 BS. Therefore it was concluded that a single dose of BIRB 796 BS, up to 600 mg, appears to be well-tolerated in healthy male subjects
Conclusions:	Total mean recovery of ^{14}C-BIRB 796 BS derived radioactivity amounted to 83.7% of dose with feces (79.4%) representing the main route of excretion compared to urine (3.55%). Total ^{14}C-radioactivity concentration (BIRB 796 BS and metabolites) declined slowly in plasma with a long elimination half-life ($t_{½}$ = 104 hr). This long half-life is presumably because of the presence of metabolite(s) with a longer half-life than the parent drug. It is not known whether this long $t_{1/2}$ value was a result of one predominant metabolite or several minor metabolites. Isolation and identification of the metabolites are on-going and the results will be reported separately [U03-3056]. The implication of this finding will be explored.