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 Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001461-28	
Name of active ingredient: BI 44370 BS		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 07 AUG 2009	**Trial No. / U No.:** 1246.14 / U09-1749-01	**Dates of trial:** 26 SEP 2008 – 31 OCT 2008	**Date of revision:** Not applicable

Title of trial:	A phase I trial to investigate the metabolism and pharmacokinetics of an open label single dose of 200 mg [^{14}C]-BI 44370 BS administered as an oral solution in healthy male volunteers
Principal Investigator:	[redacted]
Trial site:	[redacted] The Netherlands
Publication:	Data of this study have not been published.
Clinical phase:	I
Objectives:	*Primary objective* To investigate the basic pharmacokinetics of BI 44370 BS, its metabolite CD 10419 BS, and ^{14}C-radioactivity including mass balance, excretion pathways, and metabolism following a single oral administration of 200 mg [^{14}C]BI 44370 BS to healthy male volunteers *Secondary objective* To evaluate safety and tolerability following a single oral administration of 200 mg [^{14}C]BI 44370 BS to healthy male volunteers
Methodology:	Open-label absorption, distribution, metabolism and excretion study with 8 male subjects following oral administration of [^{14}C]BI 44370 BS
No. of subjects:	
planned:	Entered: 8
actual:	Entered, treated with [^{14}C]BI 44370 BS, and analysed for primary endpoint: 8
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 65 years inclusive, body mass index 18.0 to 30.0 kg/m^2 inclusive
Test product:	BI 44370 BS
dose:	200 mg containing 2.43 MBq ^{14}C-radioactivity
mode of admin.:	Oral solution
batch no.:	B071002338

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Reference therapy:	Not applicable
Duration of treatment:	One day (single dose)
Criteria for evaluation:	
Efficacy / clinical pharmacology:	*Pharmacokinetics* Individual time course profiles of ^{14}C-radioactivity in whole blood, plasma, urine and faeces Individual time course profiles of BI 44370 BS and its glucuronide metabolite CD 10419 BS in plasma and urine Rate and extent of excretion and mass balance based on the total radioactivity in urine and faeces Elucidation of metabolite structures and identification of major metabolites in plasma, urine, and faeces (if feasible) in comparison with various animal species $C_{blood\ cells}/C_{plasma}$ and C_{blood}/C_{plasma} ratios of ^{14}C-radioactivity Estimation of pharmacokinetic (PK) parameters using non-compartmental methods from: - concentrations of BI 44370 BS and CD 10419 BS in plasma and urine - concentrations of ^{14}C-radioactivity in whole blood, plasma, urine, and faeces
Safety:	Adverse events (AEs), physical examination, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG), global tolerability, and clinical laboratory tests
Statistical methods:	Descriptive statistics

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Pharmacokinetics

^{14}C- radioactivity and mass balance

Drug-related ^{14}C-radioactivity was rapidly absorbed; maximum concentrations of ^{14}C-radioactivity in plasma and whole blood were reached 0.5 h after drug administration, comparable to the t_{max} of the parent compound, BI 44370 BS. The terminal half-life of ^{14}C-radioactivity in plasma ($t_{1/2}$ 8.21 h, gCV 75.9%) was about twice as long as that of parent compound ($t_{1/2}$ 4.16 h, gCV 16.3%), suggesting the presence of at least one metabolite with a longer terminal half-life than BI 44370 BS. Most of the drug related radioactivity was found in plasma and only about one third distributed into blood cells.

Most of the total radioactivity in plasma was related to BI 44370 BS (57.8%, gCV 25.5%). The contribution of the metabolite CD 10419 BS to the total radioactivity in plasma was low (4.30%, gCV 40.1%). Consequently, about 38% of plasma radioactivity was related to one or more metabolites in addition to CD 10419 BS. The sum of the amount of CD 10419 BS and BI 44370 BS excreted in urine was about 89% of the amount of total radioactivity in urine, suggesting the presence of one or more additional metabolites in urine.

The total cumulative recovery in all subjects was 93.6% (range 91.3% to 95.8%). More than 90% of the dose was excreted within 4 days. Overall, 84.8% (gCV 2.87%) was excreted in faeces and 8.61% (gCV 20.5%) was excreted in urine.

BI 44370 BS

BI 44370 BS was rapidly absorbed with maximum plasma concentrations (C_{max}) attained 0.5 h after drug administration. BI 44370 BS followed rapid mono- or bi-exponential disposition kinetics. The $t_{1/2}$ was 4.16 h (gCV 16.3%). Renal excretion of BI 44370 BS was 7.58% of the dose.

CD 10419 BS

Plasma concentrations of CD 10419 BS were detectable 10 min after drug administration in four of eight subjects and 20 min after drug administration in the remaining four subjects, indicating rapid formation of the metabolite. Maximum plasma concentrations of CD 10419 BS were observed 1 h after dosing, only slightly delayed compared to parent compound. The $t_{1/2}$ was 1.58 h (gCV 21.0%). The ratios of CD 10419 BS to BI 44370 BS were 0.0740 (gCV 39.8%) for C_{max} and 0.0744 (gCV 46.9%) for $AUC_{0-\infty}$.

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Safety results:

After administration of 200 mg [^{14}C]BI 44370 BS to eight healthy male volunteers, five subjects (62.5%) experienced six AEs during the active treatment period. There were no serious or other significant AEs. All AEs were mild in intensity. The most frequently reported AE was pollakiuria, reported in two subjects (25.0%) during the BI 44370 BS treatment period, possibly due the fluid intake requirement of the trial. The most frequently reported system organ class of AE was gastrointestinal disorders, reported in three subjects (37.5%). One subject required therapy for an AE (eye irritation) and one subject did not recover from an AE (gingivitis) by the end of the study. The investigator did not consider any AEs possibly related to the study medication. No AEs which could have had a possible influence on PK parameters were reported. No findings of the clinical laboratory tests, ECG parameters, or vitals signs were reported as clinically relevant. Global tolerability was 'good' in all eight subjects.

Conclusions:

After single oral administration of 200 mg [^{14}C]BI 44370 BS to healthy male volunteers, the total gMean recovery of ^{14}C-radioactivity was 93.6% (84.8% in faeces and 8.61% in urine). The glucuronide metabolite CD 10419 BS was rapidly formed and rapidly eliminated. Total radioactivity exceeded the sum of BI 44370 BS and CD 10419 BS in both plasma and urine, indicating the presence of one or more additional metabolites.

Single oral doses of 200 mg [^{14}C]BI 44370 BS were safe and well tolerated in healthy male volunteers. The results of this study do not indicate any safety concerns for future trials of BI 44370 BS.