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:		**EudraCT No.:** 2006-003499-36	
Name of active ingredient: BI 44370 TA		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 29 FEB 2008	**Trial No. / U No.:** 1246.1 / U08-1167-01	**Date of trial:** 24 APR 2007 – 02 AUG 2007	**Date of revision** (if applicable)**:**

Title of trial:	Safety, tolerability and pharmacokinetics of BI 44370 TA oral drinking solution in healthy male volunteers (dose range: 5 - 800 mg). A double-blind (within dose groups), randomised, placebo-controlled within dose groups, single rising dose study, including re-dosing at 100 mg and 500 mg (solution) and at 200 mg (four 50 mg tablets).
Principal/Coordinating Investigator:	[redacted]
Trial site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim/Rhein, Germany.
Publication (reference):	Data on this study have not been published.
Clinical phase:	I
Objectives:	The objective of this trial was to evaluate the safety, tolerability and pharmacokinetics of single rising oral doses of BI 44370 TA in healthy male volunteers, to compare a 200 mg drinking solution vs. a tablet formulation and to assess intra-individual PK variability by re-dosing at 100 mg and 500 mg.
Methodology:	Randomised, double-blind, placebo-controlled within dose groups, single rising dose, single centre.
No. of subjects:	
planned:	Enrolled: 80 Entered: 64

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actual:	Enrolled: 68 Entered: 56 Completed: 55 BI 44370 TA Tablet: entered: 6 treated: 6 analysed (for primary endpoint): 6 BI 44370TA drinking solution: entered: 43 treated: 42 analysed (for primary endpoint): 42 Placebo: entered: 13 treated: 13 analysed (for primary endpoint): 13
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥21 and ≤50 years, BMI range: 18.5 and ≤29.9 kg/m2
Test product:	BI 44370 TA drinking solution
dose:	5 mg, 20 mg, 50 mg, 100 mg, 200 mg, 300 mg, 500 mg
mode of admin.:	Oral
batch no.:	Powder: B061003108; Natrosol solution for mixing: B051000359
Test product:	BI 44370 TA tablet 50 mg
dose:	200 mg (4x 50 mg tablet)
mode of admin.:	Oral
batch no.:	B071000425
Reference therapy 1:	BI 44370 TA placebo solution
dose:	Not applicable
mode of admin.:	Oral
Reference therapy 2:	Placebo matching BI 44370 TA 50 mg tablets
dose:	Not applicable
mode of admin.:	Oral

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batch no.:	Powder: B061003107; Natrosol solution with quinine sulphate: B051000544 Tablet: B071000399
Duration of treatment:	One day (single dose) for each treatment. For dose groups 100, 200 and 500 mg, a second dose was administered at least 13 days after the first dose
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Pharmacokinetic parameters: $AUC_{0-\infty}$, AUC_{0-tz}, AUC_{0-2}, $\%AUC_{tz-\infty}$, C_{max}, t_{max}, $_z$, $t_{1/2}$, $MRT_{p.o.}$, CL/F, V_z/F, AUC_{t1-t2}, $Ae_{t1/t2}$, $fe_{t1/t2}$, $CL_{R,t1/t2}$
Safety:	Physical examination, vital signs (blood pressure, pulse rate, respiratory rate, oral body temperature), 12-lead electrocardiogram, laboratory tests, adverse events and tolerability
Statistical methods:	Descriptive statistics for safety and pharmacokinetic endpoints were calculated. Dose proportionality of BI 44370 TA was explored using a regression model. A 95% confidence interval of the slope was computed. The statistical model for the analysis of relative bioavailability (re-dosing, tablet vs. solution) was an analysis of variance on the log scale.

SUMMARY – CONCLUSIONS:

Pharmacokinetic results:	In healthy male Caucasian subjects BI 44370 BS follows a mono- or bi-exponential disposition kinetics with rapid absorption and a non-linear, over proportional increase in exposure after dose increment which became less pronounced at dosages ≥ 200 mg. Accordingly, the intra-individual variability comparing the same dose given twice to the same individual became smaller at dosages beyond 100 mg and the tablet formulation of BI 44370 BS had about the same bioavailability as the solution . The terminal $t_{1/2}$ was rather short , ranging between (gMean) 3.37 and 5.04 h at dosages ≥ 100 mg BI 44370 BS. At that dose range (100 - 500 mg) $t_{1/2}$ was dose independent. The disproportional increase in exposure points to saturation processes especially during absorption and/or first pass metabolism since the $t_{1/2}$ did not change accordingly. The increment in oral bioavailability at higher dosages is further supported by the dose dependent increase in the fraction of dose excreted in urine without any dose dependency of the excretion rate.
Safety results:	BI 44370 TA administered as an oral solution or tablet was well-tolerated

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following single doses ranging from 5 to 500 mg. There was no reduction in tolerability with increasing dose. All treatments were considered safe in this study.

Acne was reported 4 days after treatment by 2 subjects who received active treatment, all other AEs were reported by subjects who received placebo. The investigator deemed that neither of the AEs observed in the treated subjects was drug related. The rate and intensity of AEs observed was low, with no apparent dose dependency. All AEs were mild in nature.

Laboratory analyses did not detect any consistent or clinically significant changes in blood or urine contents associated with the active treatment. All on-treatment means were within normal ranges. There were individual values outside normal ranges (both above and below), but these were only seen at isolated time points, were often already present at baseline, and generally distributed between placebo treatment and active treatment. There was no apparent dose dependency in these individual values outside the normal range whilst on treatment.

No clinically relevant ECG changes were observed. In particular, there is no indication of any prolongation of the QT interval of the ECG.

From the results of the safety observations, it can be concluded that BI 44370 TA was safe and well-tolerated.

Conclusions:

BI 44370 TA was rapidly absorbed after single oral administration. The PK of BI 44370 TA exhibited moderate intra-individual variability, which was less marked at doses above 100 mg. The terminal $t_{1/2}$ was short and dose-independent in the range 100-500 mg. There was an incremental increase in bioavailability at higher doses, probably due to saturation processes during absorption or first-pass metabolism.

BI 44370 TA was safe and well-tolerated at the doses administered. Adverse event rates during the study were low and none of the events was considered related to the study drug.