Clinical Study Synopsis for Public Disclosure

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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.:** 2007-003079-38	
Name of active ingredient: BI 44370 TA		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 15 OCT 2008	**Trial No. / U No.:** 1246.2/ U08-2005-01	**Dates of trial:** 23 JAN 08 – 16 APR 08	**Date of revision:** Not applicable

Title of trial:	Relative oral bioavailability of BI 44370 TA drinking solution (100 mg and 200 mg) and BI 44370 TA tablets (100 mg as two 50 mg tablets) with and without a high fat meal in healthy male and female volunteers: a single dose, open-label, randomised, six-way cross-over trial
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim/Rhein, Germany
Publication (reference):	Data on this trial have not been published
Clinical phase:	I
Objective:	The objective of this trial was to evaluate the relative oral bioavailability and pharmacokinetics of BI 44370 TA drinking solution (100 mg and 200 mg) and BI 44370 TA tablets (100 mg as two 50 mg tablets) with and without a high fat meal and to assess the safety and tolerability of the substances.
Methodology:	This was a randomised, open-label, single dose, six-way cross-over comparison, single centre trial of 3 months duration
No. of subjects:	
planned:	entered: 12
actual:	entered: 12 BI 44370 TA 100 mg and 200 mg drinking solution (fasted and fed state): entered: 12 treated: 12 (PiB100fast: 11) analysed (for primary endpoint): 12 BI 44370 TA 100 mg tablets (fasted and fed state): entered: 12 treated: 12 analysed (for primary endpoint): 12
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥21 and ≤55 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	BI 44370 TA drinking solution
dose:	A= BI 44370 TA drinking solution 100 mg fasted (=PiB100fast) B= BI 44370 TA drinking solution 100 mg fed (=PiB100fed)

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	C= BI 44370 TA drinking solution 200 mg fasted (=PiB200fast)
	D= BI 44370 TA drinking solution 200 mg fed (=PiB200fed)
mode of admin.:	Oral
batch no.:	Powder: B071003542; Solvent: B071002338
Test product:	BI 44370 TA tablet 50 mg
dose:	E= 100 mg BI 44370 BS as two tablets 50 mg fasted (=Tbl100fast)
	F= 100 mg BI 44370 BS as two tablets 50 mg fed (=Tbl100fed)
mode of admin.:	Oral
batch no.:	B071003466
Reference therapy:	Not applicable
Duration of treatment:	One day (single dose) for each treatment followed by a wash-out period of at least 10 days
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic parameters: C_{max}, $AUC_{0-2,}$ $AUC_{0-\infty}$, t_{max}, AUC_{0-tz}, , $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, $MRT_{p.o.}$, CL/F, V_z/F
Safety:	Physical examination, vital signs (blood pressure, pulse0 rate), 12-lead electrocardiogram (ECG), monitoring of adverse events, clinical laboratory (haematology, clinical chemistry), and tolerability assessment
Statistical methods:	Descriptive statistics for safety and pharmacokinetic parameters were calculated. The statistical model for the analysis of relative oral bioavailability of BI 44370 (fed and fasted) was an analysis of variance (ANOVA) on the log scale.
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	Study 1246.2 was a randomised, single dose, open-label, six-way cross-over trial to evaluate the relative oral bioavailability and pharmacokinetics of BI 44370 TA drinking solution (100 mg and 200 mg) and BI 44370 TA tablets (100 mg as two 50 mg tablets) with and without a high fat meal. Before this trial, no female subjects had been exposed to BI 44370 TA.

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A total of 12 subjects (6 males, 6 females) were randomised to receive all 6 planned doses of trial medication (PiB100fast, PiB100fed, PiB200fast, PiB200fed, Tbl100fast, Tbl100fed). All treatments were applied as planned, except that one female subject did not receive the PiB100fast treatment due to an AE not related to the trial. Thus, 71 doses of BI 44370 TA were applied during the trial.

In healthy male and female Caucasian subjects, BI 44370 BS demonstrated a prominent negative food effect, that is both dose and formulation dependent. Relative oral bioavailability when given as oral drinking solution was 8.2% for C_{max}, 16.3% for AUC_{0-tz}, and 4.9% for AUC_{0-2} for 100 mg BI 44370 BS and 15.8%, 27.6%, and 6.4% for 200 mg BI 44370 BS, respectively under fed compared to fasted condition. T_{max} was prolonged from 30 - 46 min to 3.5 hours when BI 44370 BS was given with food, however, no lag phase was observed. The reduced exposure and prolongation of t_{max} was also observed for the 50 mg tablets at a dose of 100 mg. However the effect was less pronounced than for the oral drinking solution with the relative oral bioavailability being 22.9% for C_{max}, 9.75% for AUC_{0-2}, and 28.1% for AUC_{0-tz}, and t_{max} being 1.99 h for fed compared to 37 min for fasted condition. Under fasted condition, both formulations showed equivalent bioavailability at a dose of 100 mg. The pharmacokinetics of BI 44370 BS was influenced by gender in a dose dependent way with female subjects showing higher exposure than males, even after adjustment for bodyweight or BMI at about the same terminal half life. The effect was more pronounced after administration of 200 mg BI 44370 BS than after administration of 100 mg BI 44370 BS. However, the observed differences were mainly driven by a single female volunteer showing 2 - 4 times higher exposure with all treatments than all other volunteers. The reason for this subject having higher exposure to BI 44370 than all other volunteers is currently unknown.

Safety results:

BI 44370 TA administered as an oral solution or tablet was generally well-tolerated. All treatments were considered safe in this trial.

In total, 7 (3 males, 4 females) out of the 12 subjects (58.3%) reported adverse events (AEs) during the course of the trial; overall 18 AEs were reported. Of those, 1 male subject reported one AE during the treatment period, 4 female subjects reported AEs during the treatment periods and wash-out phases and 2 male subjects reported AEs only in the wash-out phase.

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The AEs observed were mild or moderate in intensity, none was of severe intensity. Five (5) subjects (1 male, 4 females) required therapy for their AEs.

No serious AEs or other significant AEs (according to ICH E3) occurred during the trial. All AEs had resolved by the end of the trial.

The most frequently reported AEs by preferred term were headache (41.7% of subjects) and nasopharyngitis (33.3% of subjects). Other AEs reported by 1 subject each were migraine, pharyngitis, sinusitis, erythema, nervousness and pharyngolaryngeal pain. Of those, 4 AEs in 2 subjects were considered drug-related by the investigator. One female subject reported migraine of moderate intensity during treatment period 1 (PiB100fast), and headache of moderate intensity during treatment periods 2 (PiB100fed) and 5 (Tbl100fast), all of these episodes required therapy. This subject had migraine as baseline condition. The episode of migraine started 6 hours after dosing and lasted for 45 hours. The episodes of headache started 4 hours and 5 hours after dosing and lasted for 7 hours and 4 hours, respectively. One male subject reported mild facial erythema (ten spots with about 1 cm diameter, no papules) in treatment period 5 (PiB100fast) starting 28 hours after dosing and lasting for 52 hours. This AE resolved without therapy. All other AEs were considered to be not trial drug related.

No change of laboratory parameters was recorded as an AE. The laboratory analysis did not detect any consistent or clinically significant changes in blood or urine contents associated with the treatment. The majority of the laboratory values were within the normal reference ranges. No significant transitions relative to reference range occurred. There were individual values outside normal ranges but these were mostly present at isolated time-points and were often already present at baseline.

No clinically relevant ECG findings occurred in this trial. In particular, there is no indication of any prolongation of the QT interval of the ECG.

No relevant de-or increases in vital signs (blood pressure, pulse rate) were observed.

The overall global tolerability was rated as good for 83.3% of the subjects. In 2 subjects the tolerability was rated as satisfactory due to the occurrence of AEs.

In summary, the rate and intensity of AEs observed was low.

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	The majority of the AEs occurred under treatment with BI 44370 TA drinking solution 100 mg in the fasting state (3 AEs) and in the fed state (2 AEs). One AE occurred under treatment with BI 44370 TA tablets 100 mg in the fasting state and 2 AEs occurred in the fed state. Ten (10) AEs occurred in the wash-out phases. No AEs occurred under treatment with BI 44370 TA 200 mg drinking solution.
Conclusions:	In healthy male and female Caucasian subjects, BI 44370 BS demonstrated a prominent negative food effect, that is both dose and formulation dependent. Overall exposure (AUC), peak exposure (C_{max}), and time to peak exposure (t_{max}) are affected. The relative oral bioavailability of 100 mg and 200 mg BI 44370 BS under fed condition was 5 - 28% compared to fasted condition with the tablet being less affected than the oral drinking solution and the higher dose being less affected than the lower dose. The pharmacokinetics of BI 44370 BS was influenced by gender in a dose dependent way with female subjects showing higher exposure than males. The effect was more pronounced after administration of 200 mg BI 44370 BS than after administration of 100 mg BI 44370 BS. Due to the low number of subjects and AE episodes, the absence of a placebo group and the open label design, the conclusions that can be drawn are limited. In general, all treatments investigated were safe and tolerated well, independent of dose, formulation, meal status, and gender. From the AEs in this trial there is no concern for further clinical investigations of the doses tested, given that all related events were of mild or moderate intensity and resolved completely. In future clinical trials the kind of AEs that were assessed as drug related in this trial (headache and erythema) may need special attention.