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: Not applicable		**EudraCT No.:** 2008-005946-21	
Name of active ingredient: BI 44370 TA		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 FEB 2010	**Trial No. / U No.:** 1246.15 / U10-1169-01	**Dates of trial:** 30 JAN 2009 – 08 JUN 2009	**Date of revision:** Not applicable

Title of trial:	Safety, tolerability and pharmacokinetics of multiple rising oral doses of BI 44370 TA tablets (100 mg, 200 mg and 300 mg three times every two hours on one day and q.d. for another 2 to 3 days) in healthy male and female volunteers, a randomised, double-blind, placebo-controlled within dose groups Phase I study
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim/Rhein, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	Evaluation of safety, tolerability and pharmacokinetics of multiple rising oral doses of BI 44370 TA in healthy male and female volunteers
Methodology:	Randomised, double-blind, placebo-controlled within dose groups, multiple rising dose trial
No. of subjects:	
planned:	Randomised: 36
actual:	

	Randomised	Treated	Analysed for primary endpoint
Placebo	12	12	11
BI 44370 100 mg	7	7	7
BI 44370 200 mg	8	8	8
BI 44370 300 mg	7	7	7
Total	34	34	32

Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age 21 to 50 years inclusive, body mass index 18.5 to 29.9 kg/m^2 inclusive

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Test product:	BI 44370 tablets 100 mg and 200 mg	
dose:	100 mg, 200 mg, and 300 mg	
mode of admin.:	Oral	
batch no.:	BI 44370 100 mg BI 44370 200 mg	B081001521 B081001456
Reference therapy:	Placebo matching BI 44370 100 mg and 200 mg tablets	
dose:	Not applicable	
mode of admin.:	Oral	
batch no.:	Placebo for BI 44370 200 mg Placebo for BI 44370 200 mg	B081001963 B081001896
Duration of treatment:	A total of 4 days for BI 44370 or placebo over 2 treatment periods with a wash-out period of at least 70 h between treatment periods. • Treatment Period 1 (single dose period): 1 day • Treatment Period 2 (multiple dose period): 3 days (3 doses on Day 1 at 0, 2, and 4 h and 1 dose on Days 2 and 3 (and 1 additional dose on Day 4 if a washout after Day 1 was required)	
Criteria for evaluation:		
Pharmacokinetics:	Pharmacokinetic (PK) parameters for BI 44370 BS and its glucuronide (BI 44370 GLUC), if feasible: After the first dose: C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, $\%AUC_{tz-\infty}$, AUC_{0-2}, AUC_{0-24}, AUC_{0-tz}, AUC_{t1-t2}, λ_z, $t_{1/2}$, $MRT_{p.o.}$, CL/F, V_z/F, Ae_{0-24}, fe_{0-24}, $CL_{R,0-24}$ After the last dose on Day 1/Treatment Period 2: $C_{max,N}$, $t_{max,N}$, $AUC_{0-2,N}$, $AUC_{t1-t2,N}$, $AUC_{0-tz,N}$, $AUC_{0-\infty,N}$, $\%AUC_{tz-\infty,N}$, $\lambda_{z,N}$, $t_{1/2,N}$, $MRT_{p.o.,N}$, $CL/F_{,N}$, $Vz/F_{,N}$, $Ae_{0-24,N}$, $fe_{0-24,N}$, $CL_{R,0-24,N}$, and accumulation ratios ($R_{A,AUC,N}$, $R_{A,Cmax,N}$) After the last multiple dose: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{0-2,ss}$, $AUC_{0-24,ss}$, $AUC_{t1-t2,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $Vz/F_{,ss}$, $Ae_{0-24,ss}$, $fe_{0-24,ss}$, $CL_{R,0-24,ss}$, accumulation ratios ($R_{A,AUC}$, $R_{A,Cmax}$), and linearity index	

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Safety:	Physical examination Vital signs: blood pressure, pulse rate, respiratory rate, oral body temperature, and orthostasis test 12-lead electrocardiogram (ECG) Clinical laboratory tests, including haematology, clinical chemistry, urinalysis, and testing of faecal occult blood Adverse events (AEs) Assessment of tolerability by investigator
Statistical methods:	Descriptive statistics for safety and PK endpoints were calculated. Dose proportionality of BI 44370 BS was explored using a regression model. The 95% confidence interval for the slope was computed. Linearity with respect to multiple doses of BI 44370 TA using $AUC_{0-\infty}$ and $AUC_{\tau,ss}$ was assessed using a linear model on the logarithmic scale including 'subject' and 'order' as fixed effects. Pair-wise comparisons of $AUC_{\tau,ss}$ and $AUC_{0-\infty}$ provided the linearity indices including a 2-sided 95% confidence interval. To investigate if steady state was attained, the trough concentrations of BI 44370 BS were analysed by a mixed linear model with 'time' as a repeated effect. Subsequently, pair-wise comparisons of the differences between all time points were performed using t-tests.
SUMMARY – CONCLUSIONS:	
Pharmacokinetic results:	Of the 34 treated subjects, 32 subjects completed the treatment according to the protocol and 2 subjects discontinued treatment prematurely. One subject in the placebo group erroneously received 1 dose of BI 44370 100 mg. The subjects in this trial comprised 18 males (52.9%) and 16 females (47.1%). The median age, height and weight were 35 years, 175.0 cm and 73.0 kg. The dose groups were balanced with respect to sex, age, height, and weight. BI 44370 BS showed a more than dose-proportional increase in exposure (AUC) and maximum plasma concentration (C_{max}) in the dose range of 100 to 300 mg after single or multiple administration. Plasma concentrations of BI 44370 BS

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Name of active ingredient: BI 44370 TA		**Page:** 4 of 6	**Synopsis No.:**
Module:		**Volume:**	
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reached steady state after 5 to 6 doses in the 200 and 300 mg dose groups; however, in the 100 mg dose group, plasma concentrations of BI 44370 BS were too low to draw any conclusions on attainment of steady state. Maximum plasma concentrations of BI 44370 BS were reached between 1 and 3 h after either single or multiple oral administration. BI 44370 BS showed high accumulation when administered every 2 h ($R_{A,AUC0-24}$ was 4.48 for 100 mg t.i.d., 4.45 for 200 mg t.i.d., and 2.26 for 300 mg b.i.d.) but modest accumulation after once daily dosing ($R_{A,AUC0-24}$ was 1.29 for 100 mg, 1.58 for 200 mg, and 1.27 for 300 mg).

After multiple dosing, clearance of BI 44370 BS was dose-dependent, decreasing from 2400 mL/min (100 mg) to 818 mL/min (300 mg). Renal excretion of the parent compound was a minor elimination pathway and increased from about 5.68% of the total clearance at a dose of 100 mg daily to about 16.4% of the total clearance at 300 mg daily. The volume of distribution of BI 44370 BS decreased with an increase in dose from 637 L (100 mg) to 275 L (300 mg) after multiple administration of BI 44370 TA. The terminal half-life of BI 44370 BS at steady state was relatively constant, ranging from 3.03 to 4.11 h.

Exposure was higher in female subjects than male subjects. After multiple doses of BI 44370 TA, the gMean female:male $AUC_{0-24,ss}$ ratio ranged from 1.08 (300 mg) to 1.81 (100mg).

Following multiple oral dosing of BI 44370 TA (1 single dose day and, following a washout of at least 70 hours, 5 or 6 multiple doses on 3 days), the gMean metabolite ratios of BI 44370 GLUC to BI 44370 ranged from 0.0771 (100 mg) to 0.108 (200 mg) for AUC_{0-24} and from 0.0777 (100 mg) to 0.134 (200 mg) for C_{max}. After single or multiple dosing of BI 44370 TA, increases in exposure (AUC and C_{max}) to BI 44370 GLUC were more than proportional with dose.

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Safety results:

Thirty-four subjects were treated in this trial. In the placebo group, 10 subjects each received 6 doses of placebo, 1 subject received 5 doses of placebo, and 1 subject received 5 doses of placebo and 1 erroneous dose of BI 44370 100 mg. In the BI 44370 treatment groups, 7 subjects each received 6 doses of 100 mg, 8 subjects each received 6 doses of 200 mg, 6 subjects each received 5 doses of 300 mg and 1 subject received 1 dose of 300 mg.

Treatment-emergent AEs were reported in 14 subjects (41.2%). All AEs were mild or moderate in intensity. There were no deaths, serious AEs, or other significant AEs. After a single dose of study medication in Treatment Period 1, the number of subjects who experienced at least 1 AE was lower in the BI 44370 groups (0 to 14.3%) than in the placebo group (25.0%). After multiple doses of BI 44370 in Treatment Period 2, the frequencies of subjects who experienced at least 1 AE in the BI 44370 groups were 57.1% for 100 mg, 37.5% for 200 mg, and 28.6% for 300 mg). In the placebo group, 2 subjects (16.7%) experienced an AE in Treatment Period 2; however, 1 of these subjects experienced an AE (fungal skin infection) after having erroneously received 100 mg BI 44370.

The AE by MedDRA preferred term reported in the highest overall frequency of subjects was headache, experienced by 3 subjects (8.8%), all during Treatment Period 2 (2 subjects treated with BI 44370 and 1 subject treated with placebo). All other AEs were reported in 1 subject each. The investigator considered headache (BI 44370 200 mg t.i.d.) and papular rash (BI 44370 200 mg q.d.) to be possibly related to the study medication. One subject discontinued treatment with study medication due to moderate vertigo after a single dose of BI 44370 300 mg. The investigator did not consider this AE to be possibly related to the study medication.

No laboratory values were considered clinically relevant. The faecal occult blood test was positive in 1 subject treated with BI 44370 who had experienced haemorrhoids. This finding was reported as an AE but was not considered drug-related. No clinically relevant treatment-related changes in ECG parameters were seen.

The investigator assessed global tolerability of the study medication as ‘satisfactory’ in 1 subject treated with a single dose of BI 44370 300 mg and 2 subjects treated with BI 44370 200 mg t.i.d. and ‘good’ in all other subjects.

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Conclusions:

Both BI 44370 BS and its metabolite BI 44370 GLUC showed more than dose proportional increases in exposure (AUC) and maximum plasma concentration (C_{max}) in the dose range of 100 to 300 mg after single or multiple administration of BI 44370 TA. Plasma concentrations of BI 44370 BS reached steady-state in the 200 mg and 300 mg but not the 100 mg dose groups. Multiple doses of BI 44370 100 or 200 mg t.i.d. or 300 mg b.i.d. were well tolerated by healthy male and female volunteers. The results of this trial do not indicate any safety concerns for the future development of BI 44370.