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.:** 2009-014890-42	
Name of active ingredient: BI 113823		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 NOV 2010	**Trial No. / U No.:** 1272.1 / U10-2829-01	**Dates of trial:** 19 JAN 2010 – 04 JUN 2010	**Date of revision:** Not applicable

Title of trial:	Investigation of safety, tolerability and pharmacokinetics of single rising oral doses of 5 to 800 mg BI 113823 Powder in Bottle (PiB) and tablet administered to healthy male volunteers in a partially randomised and double-blinded, placebo-controlled phase I trial. Including intra-individual open comparisons of PiB and tablet (fasted and fed)
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre of Boehringer Ingelheim, Biberach, Germany
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	The objectives of this trial were to investigate the safety, tolerability, and pharmacokinetics (PK) including dose proportionality of BI 113823, as well as the relative bioavailability (BA) of solution (PiB) vs. tablet and the food effect for the tablet (fasted and fed).
Methodology:	This was a single rising dose (SRD), partially randomised and double-blinded, placebo-controlled single-centre trial including intra-individual comparisons of PiB vs. tablet and tablet under fasted vs. fed conditions.
No. of subjects:	
planned:	Entered : 72 subjects (For each of the 9 planned dose groups: 6 subjects on BI 113823 and 2 subjects on placebo)
actual:	Entered: 63 subjects (In the first dose group, one subject who was supposed to receive placebo was missing due to illness and could not be replaced. Thus, only 7 subjects received trial medication. In addition, dose group 9 was cancelled because the stopping criterion for dose escalation was met)

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	Solution, treatment 1- 6 (5, 10, 20, 50, 100, and 200 mg PiB): BI 113823: entered: 36 treated: 36 analysed (for primary endpoint): 36 Placebo: entered: 11 treated: 11 analysed (for primary endpoint: 11 Tablet, treatment 5a (100 mg fasted), 5b (100 mg fed), 7 (400 mg), and 8 (600 mg): BI 113823: entered: 18 treated: 18 analysed (for primary endpoint):18 Placebo: entered: 6 treated: 6 analysed (for primary endpoint: 6 Subjects of dose group 5 received 3 single doses of 100 mg BI 113823 or placebo (treatments 5, 5a, 5b), all other subjects received 1 single dose of BI 113823 or placebo
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥18 and ≤45 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	BI 113823
doses:	5, 10, 20, 50, 100, and 200 mg as solution (PiB), 100, 400 and 600 mg as film-coated tablets (the 800 mg dose was intended, but not performed because the pre-defined stopping criterion was fulfilled.)
mode of admin.:	Fasted: oral administration, with 240 mL water after an overnight fast of at least 10 h Fed: oral administration, with 240 mL water after an overnight fast of at least 10 h, and after a high-fat breakfast
batch nos.:	Tablet: 50 mg: B091004161, 100 mg: B091004163, powder for oral solution 200 mg: B091004003, solvent for oral solution (0.4% Sucralose): B091003854
Reference therapy:	Placebo solution and tablet
doses:	Not applicable
mode of admin.:	Fasted: oral administration, with 240 mL water after an overnight fast of at least 10 h Fed: oral administration, with 240 mL water after an overnight fast of at least 10 h, and after a high-fat breakfast

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batch nos.:	Placebo for 50 mg tablet: B091004148, for 100 mg tablet: B091004160, for oral solution: B091004004, solvent for oral solution (0.015% Sucralose): B091003852
Duration of treatment:	Three single doses with a washout period of at least 7 days between each administration for subjects receiving treatments 5, 5a and 5b (100 mg BI 113823 or placebo, administered as solution for treatment 5 or as tablet for treatments 5a and 5b); one single dose for subjects receiving treatments 1 to 4, 6, 7, and 8.
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic parameters: C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$
Safety:	The safety evaluation was based on adverse events (AEs), laboratory tests, physical examinations, vital signs (blood pressure, pulse rate), ECGs and the tolerability assessment by the investigator
Statistical methods:	Descriptive statistics for safety and PK endpoints were calculated. Dose proportionality was explored by using a regression model. A 95% confidence interval (CI) for the slope was computed (for parameters AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max}). The relative BA of the tablet and the solution, as well as the food effect of the tablet were investigated by applying the average bioequivalence method to the ratio between PK parameters (AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max}) of the 2 respective treatments. Point estimates (geometric means) of the intra-subject ratios and their 2-sided 90% CIs were calculated. An analysis of variance (ANOVA) model on the log-transformed parameters including effects for 'subject' and 'treatment' was used. CIs were based on the residual error from ANOVA.
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	Following administration of a single oral dose to healthy male Caucasian subjects with a mean age of 32.5 years and a mean BMI of 24.90 kg/m^2, BI 113823 was rapidly absorbed. The time point of maximum plasma concentrations ranged from 30 minutes to 4 h (5 to 20 mg) and from 15 minutes to 2 h (50 to 200 mg) after administration as solution (PiB). Following administration as tablet, t_{max} ranged from 30 minutes to 2 h (100 to 600 mg).

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Clinical pharmacology results, cont.:

Exposure (C_{max}, AUC_{0-tz}, $AUC_{0-\infty}$) to BI 113823 increased slightly more than dose proportionally over the entire dose range from 5 to 600 mg. Regarding doses ≥ 50 mg, dose proportionality can be assumed. Double plasma peaks were detected in the lower dose groups and became less pronounced at doses ≥50 mg. After attainment of t_{max}, plasma concentrations declined rapidly in a biphasic manner. The terminal $t_{1/2}$ ranged between (gMean) 6.47 and 10.3 h at doses ≥50 mg of BI 113823. Following the administration as a single dose, BI 113823 had a limited urinary excretion (gMean fe_{0-24}: 4.85 to 10.3%).

Under fasting conditions, for the 100 mg tablet formulation the extent of exposure was similar to the PiB (solution) formulation as determined by AUC_{0-tz} and $AUC_{0-\infty}$, but C_{max} was approximately 29% higher than for the PiB (solution) formulation. Administration under fed conditions caused a reduction in the rate of absorption of BI 113823 indicated by a prolongation in median t_{max} from 1.00 to 3.00 h and a decrease in C_{max} of approximately 36%, but had no influence on the extent of absorption (AUC_{0-tz}, $AUC_{0-\infty}$).

Safety results:

No deaths and no AEs leading to discontinuation of trial drug occurred.

Overall, 24 out of 63 subjects (38.1%) reported AEs during the conduct of the trial. Seven AEs in 7 subjects (11.1%) were regarded as drug-related. Those AEs were headache, reported in 6 out of the 7 subjects under treatment with BI 113823 400 mg tablet (2 subjects) and Placebo PiB (4 subjects). One of the 7 subjects reported testicular pain in the washout/post-treatment phase. All AEs were of mild or moderate intensity and all subjects recovered without any specific treatment, except for subject [redacted] (SAE, see below). The AEs with the highest frequency overall were headache, observed in 10 subjects (15.9%) and nasopharyngitis, observed in 9 subjects (14.3%). All other AEs observed on BI 113823 or placebo occurred with a frequency of less than 5%.

In the SRD-part and in the BA-part, there was no indication of consistent differences in the treatment with active drug and placebo and there was no trend towards higher frequencies of AEs with ascending doses of BI 113823, neither with the solution (PiB) nor with the tablet, nor in fasted and fed condition.

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Safety results, cont.:	One SAE, which was considered to be not drug-related, occurred in subject [redacted]. The subject had received 3 single doses of 100 mg BI 113823 as drinking solution and as tablet in fasted and fed condition on 3 separate days. Seventy-two hours after last drug administration (100 mg tablet fed), the subject showed a previously not observed paroxysmal lone atrial fibrillation at the end-of-study examination. Follow-up including repeated Holter-ECG recordings (over 72 and 120 h) showed several self-limiting episodes of atrial fibrillation (duration from seconds up to approx. 1 h) even 17 days after last study drug administration. The subject did not recover from this SAE by the end of the trial; however the investigator considered the follow-up of this event as sufficient. None of the performed and centrally analysed ECGs showed any relevant changes, in particular, no prolongation of the QRS or PR interval. No clinical signs of an allergic reaction and no consistent changes in any laboratory parameters or vital signs were seen during the conduct of the trial. The global tolerability was assessed as 'good' for all subjects, except for subject [redacted], who suffered from the SAE described above. In this subject, the tolerability was assessed as 'not satisfactory'. Overall, the safety data of this trial confirm that single doses of up to 600 mg of BI 113823 were safe and well tolerated in healthy male subjects.
Conclusions:	BI 113823 was rapidly absorbed and exposure (C_{max}, AUC_{0-tz}, $AUC_{0-\infty}$) to BI 113823 increased slightly more than dose proportionally. The gMean of the terminal $t_{1/2}$ ranged between 6.47 to 10.3 h and renal elimination of unchanged drug was limited (gMean fe_{0-24}: 4.85 to 10.3%). From the results of the safety observations in both, the SRD-part and the BA-part of the trial, it can be concluded that BI 113823 was safe and well tolerated in healthy male subjects. In summary, the results of this trial support the further development of BI 113823.