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.:** 2005-004213-15	
Name of active ingredient: BI 11634		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 FEB 2009	**Trial No. / U No.:** 1234.1 / U08-2312-01	**Date of trial:** 15 NOV 2006 – 21 MAR 2007	**Date of revision** (if applicable)**:**

Title of trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of 5, 10, 25, 50, 100, 200 and 400 mg BI 11634 solution administered to healthy male volunteers. Randomised, doubleblind, placebo controlled at each dose level. Intra-individual comparison of solution to an immediate release tablet formulation at one dose level (50 mg)
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted] Germany
Publication (reference):	None as of the date of this clinical study report
Clinical phase:	I
Objectives:	First evaluation of safety, tolerability, pharmacokinetics and the pharmacodynamic effect of BI 11634 on coagulation parameters
Methodology:	Randomised, double-blind, parallel group design with single rising doses, placebo-controlled at each dose level. Intra-individual comparison of solution to an immediate release tablet formulation at one dose level not done according to amendment 3.
No. of subjects:	
planned:	entered: 56 subjects
actual:	enrolled: 56 subjects Six on active drug (BI 11634 oral solution) and 2 on placebo at each of 7 dose levels.
Diagnosis and main criteria for inclusion:	Healthy male subjects, aged ≥18 to ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	BI 11634 solution
dose:	0.5, 1, 2.5, 5, 10, 25, 32 mg solution (according to Amendment no. 3)
mode of admin.:	Oral administration after an overnight fast with ≈240 mL water
batch no.:	Powder for oral solution: B061000403

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Reference therapy:	BI 11634 placebo solution
dose:	None
mode of admin.:	Oral administration after an overnight fast with ≈240 mL water
batch no.:	B061000402
Duration of treatment:	Single dose
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Pharmacodynamics: Coagulation tests including conventional aPTT, INR, anti FXa assays and specialised (RVV/endogenous thrombin potential (ETP)) Pharmacokinetics: Plasma concentration time profiles of BI 11634 pharmacokinetics (dose proportionality, terminal half life, renal excretion) Relative bioavailability of experimental solid immediate release formulation to solution
Safety:	Physical examination, vital signs (blood pressure and pulse), ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Descriptive statistics, linear models
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	**Pharmacokinetic results:** After a single oral dose of BI 11634 in PIB solution, the plasma BI 11634 concentrations rapidly increased with a median time to maximum concentration of 0.5 hours; after attainment of the peak, the plasma levels of BI 11634 declined rapidly, displaying a mean short half-life of 2 hours. For the oral dosing of 0.5, 1, 2.5, 5, 10, 25 and 32 mg in PIB solution, the mean area under plasma concentration curves from 0 to infinity ($AUC_{0-\infty}$) were 22.3, 63.9, 135, 274, 640, 1410, and 1600 h•nmol/L, respectively; and the mean maximum concentrations were 11.8, 22.3, 55.3, 116, 256, 541 and 616 nmol/L, respectively. Over the dose range of 0.5 to 32 mg, an approximately proportional increase in $AUC_{0-\infty}$ and C_{max} with increasing dose was observed. The mean cumulative urinary excretion

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of BI 11634 (fe_{0-48}) was ranged from 4.21% to 7.06% for the studied dose of 0.5 to 32 mg without any dosing-renal excretion relationship. The low Fe values showed that renal clearance contributed to a very small proportion of the overall clearance. The urinary excretion of BI 11634 for most of the subjects was complete by 24 hours.

Pharmacodynamic results

The traditional coagulation tests such as aPTT, PRT, and PT-INR appeared to be insensitive to plasma BI 11634 concentration. However, HEPTEST was a sensitive coagulation test: over the studied dose of 0.5 to 32 mg, the mean maximum prolongation of coagulation time by HEPTEST ratio ranged from 1.17 to 2.90. There was a direct non-linear relationship between plasma BI 11634 concentration and HEPTEST results. The Heptest ratio correlated well with squared root of plasma BI 11634 concentration with R^2= 0.93.

Over the studied dose of 0.5 to 32 mg, inhibition of endogenous factor Xa activity by Russell's viper Venom (RVV) test was in the range of 7.52% to 95.2%. At 25 mg, the inhibition of endogenous activity was 95% already. The PK/PD relationship was a direct non-linear one can be best described by a sigmoid Imax model. With full range of inhibition in the studied doses and predictable PK/PD relationship, RVV inhibition appeared to be an ideal biomarker to be monitored the inhibition of endogenous FXa activity. The inhibition of FXa activity for BI 11634 was also studied with COAMATIC© test, the inhibition was correlated well with plasma BI 11634 levels, and however, for given dose of 0.5 to 32 mg, the mean range of maximum inhibition was 2.76% to 52.20%. At the highest studied, there was only 52% of the inhibition of FXa activity by BI 11634 using COAMATIC© test.

The endogenous thrombin related biomarkers namely, inhibition of endogenous thrombin potential (ETP), inhibition of thrombin peak, relative change in time to maximum thrombin inhibition (t_{tpeak}), and lag time prolongation of thrombin generation (lagtime), were evaluated in this study also. All these biomarkers were in good accordance with plasma BI 11634 plasma concentration. For the studied dose of 0.5 to 32 mg, the mean maximum inhibition of ETP was in the range of the 5.99% to 39.2%; the mean maximum peak inhibition of thrombin was in the range of 5.28% to 86.6%; the relative change in time to peak inhibition was from 1.10 fold to 2.82 fold; the prolongation of lag time of thrombin generation was in the range of 1.14 to 3.05. In the highest dose of 32

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mg, there was only 39% of inhibition of ETP, suggesting this biomarker was not quite sensitive to BI 11634 plasma levels. Of these biomarker evaluated, inhibition of thrombin peak appeared to be the better one; the PK/PD relationship of inhibition of thrombin peak can be described by an Imax model shape curve.

Safety results:

Safety results:

The frequency of AEs, related to the investigational product, was noteworthy low and the type of AEs considered by the investigator to be related to the investigational product comprised the symptoms headache and diarrhoea.

Laboratory data and vital signs did not reveal any noteworthy changes over time and when compared between the ascending dose groups.

Extensive evaluation of ECG did not show any notable changes or new ECG findings in the ascending dose groups. QTc evaluation with regard to QTcB, QTcF, QTc population and uncorrected QT intervals were without any noteworthy or clinically relevant findings. No influence of the drug on these parameters was identified after single ascending doses of BI 11634 in the range of 0.5 to 32 mg.

Conclusions:

Safety:

Overall, safety and tolerability after treatment with single ascending doses in the range of 0.5 mg to 32 mg BI 11364 could be considered as good and well tolerated.
Most often, headache was reported as AE: In the 1 mg dose group, one subject reported mild headache and one reported moderate headache. Also in the 25 mg dose group, one case of mild headache was reported. In addition one subject reported mild diarrhoea after intake of 32 mg BI 11634. No further types of AEs were reported. Neither the type nor the intensity of the AEs showed any relation to the ascending doses of BI 11634.

Laboratory values, vital signs and ECG recordings did not show any noteworthy deviations, which could be related to BI 11634. No relationship between dose and increase of deviation became apparent.

Pharmacokinetic:

Following single oral administration of BI 11634 drinking solution, the plasma

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BI 11634 levels rapidly increased and declined, displaying a short terminal half-life approximately 2 hours. Over the studied dose range of 0.5 to 32 mg, the BI 11634 displayed linear pharmacokinetics. The renal clearance contributed a very small portion of the overall clearance (4–7% of 39–53 L/h).

Pharmacodynamic:

The traditional coagulation test such as aPTT, PRT, and PT-INR appeared to be insensitive to plasma BI 11634 concentration. However, HEPTEST was a sensitive coagulation test in terms of response range and correlation with plasma concentration. In addition, inhibition of endogenous factor Xa activity by Russell's viper Venom (RVV) test appeared to be a sensitive biomarker to for BI 11634. The inhibition of thrombin peak also showed good correlation with Plasma BI 11634 and full range of response in the studied doses.

Overall:

BI 11634 given as single doses in the dose range of 0.5 to 32 mg was safe and well tolerated.