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: Not applicable		**EudraCT No.:** 2007-001266-33	
Name of active ingredient: BI 11634		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 April 2009	**Trial No. / U No.:** 1234.12 / U09-1307-01	**Dates of trial:** 31 MAY 2007 – 09 JUL 2007	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of 10 mg BI 11634 immediate release (IR) tablet compared to 10 mg of oral solution following oral administration in healthy male volunteers (open-label, single-dose, intra-individual comparison); determination of pharmacokinetics of 5 mg, 10 mg and 25 mg IR-tablet formulation (open-label, single-dose)
Principal Investigator:	[redacted]
Trial sites:	[redacted] Germany
Publication (reference):	Data of this study has not been published.
Clinical phase:	I
Objectives:	• Characterisation of the relative bioavailability of the IR-tablet vs. oral drinking solution (no primary endpoint in a statistical sense) • Safety and tolerability of the IR-tablet formulation and solution • PK profile of the single ascending doses of the IR-tablet formulation (including analysis of dose proportionality)
Methodology:	Open-label, parallel-group, single rising dose design with three dose levels; at one dose level open-label, intra-individual comparison of two formulations
No. of subjects:	
planned:	entered: 24
actual:	enrolled: 24 Treatment BI 11634 oral solution: entered: 12 treated: 12 analysed for bioavailability: 12 Treatment BI 11634 IR-tablet: entered: 24 treated: 24 analysed for bioavailability: 12 analysed for dose proportionality: 24
Diagnosis and main criteria for inclusion:	Healthy male subjects were included if they were between 18 and 50 years of age and had a BMI of $\geq$18.5 and $\leq$29.9 kg/m^2.

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Test product:	BI 11634 IR-tablet
dose:	5 mg, 10 mg, and 25 mg BI 11634
mode of admin.:	oral administration after an overnight fast with 240 mL water
batch no.:	5 mg tablets: B071000204 10 mg tablets: B071000270
Reference therapy:	BI 11634 powder for preparation of a drinking solution (reconstituted solution: 200 mg BI 11634 powder diluted in 80 mL tartaric acid 0.5%)
dose:	10 mg BI 11634 diluted ad 160 mL (4 mL of reconstituted solution plus 156 mL water)
mode of admin.:	oral administration after an overnight fast followed by 80 mL water
batch no.:	powder for preparation of a drinking solution: B071000822 tartaric acid solution: B050404
Duration of treatment:	One day (single dose administered orally) for each treatment
Criteria for evaluation:	
Clinical pharmacology:	*Pharmacodynamics:* Coagulation tests including aPTT, PT-INR, anti-factor Xa assays and further parameter such as HepTest®, COAMATIC© test, and Russell's Viper Venom test (RVV) as well as endogenous thrombin potential (ETP) and related biomarkers *Pharmacokinetics:* - primary endpoints: $AUC_{0-\infty}$, C_{max} - secondary endpoints: AUC_{0-tz} , t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F
Safety:	Physical examination, vital signs (BP, PR), ECG, laboratory tests, monitoring for adverse events, and assessment of general tolerability
Statistical methods:	Relative bioavailability (based on C_{max} and $AUC_{0-\infty}$) was assessed by means of an ANOVA on the logarithmic scale including 'formulation', 'subject', and 'period' as factors. Point estimates (geometric mean, gmean) and interval estimates for the median intra-subject ratios of test (IR-tablet) / reference (solution) were derived. Dose proportionality was analysed using a linear regression model on log-transformed data. Descriptive statistics for all other PK, PD, and safety parameters were calculated.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Pharmacokinetics

BI 11634 was rapidly absorbed, resulting in a median t_{max} ranging from 0.509 to 1.05 h. After attainment of C_{max}, the mean plasma concentrations declined rapidly, displaying mean terminal half-lives of 2.42 to 2.59 h:

BI 11634 Treatment	$AUC_{0-\infty}$ (h.nmol/L)		C_{max} (nmol/L)		$t_{1/2}$ (h)		t_{max} (h)	
	arithm. mean	CV%	arithm. mean	CV%	arithm. mean	CV%	median	range
IR-tablet 5 mg, n = 6	263	15.7	126	33.7	2.42	28.4	0.509	0.500-1.52
10 mg, n = 12	523	22.4	228	26.4	2.58	20.9	0.509	0.467-1.02
25 mg, n = 6	1020	28.5	345	16.0	2.59	48.3	1.05	0.550-1.50
Solution 10 mg, n = 12	566	24.8	200	22.0	2.33	15.4	0.517	0.500-1.50

Dose proportionality:

Dose proportionality could not be concluded for the entire dose range of 5 mg to 25 mg of BI 11634 IR-tablets. There was no evidence to conclude a deviation from dose proportionality between 5 mg and 10 mg BI 11634 administered as IR-tablets (slope estimates in paired comparisons of 5 mg and 10 mg $AUC_{0-\infty}$ 0.97, C_{max} 0.88).

Relative bioavailability:

The gmean ratios (IR-tablet/solution) were 93.01% (90% CI: 88.40, 97.87) for $AUC_{0-\infty}$ and 113.03% (90% CI: 100.21, 127.48) for C_{max}. With respect to $AUC_{0-\infty}$, the IR-tablet was bioequivalent to the solution as gmean ratio and CI% were completely contained in the 80-125% equivalence interval. C_{max} was slightly greater for the tablet than for the solution; the C_{max} upper boundary of 90% CI was slightly outside 125%.

Pharmacodynamics

HepTest® qualified as sensitive biomarker of coagulation time and RVV inhibition seemed ideal to monitor inhibition of endogenous factor Xa activity induced by BI 11634. Moreover, the biomarkers related to endogenous thrombin formation were in good accordance with BI 11634 plasma levels; ETP was less sensitive than inhibition of thrombin peak.

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Clinical pharmacology results (cont):	*Coagulation tests:* HepTest® ratio indicated a mean maximum prolongation of coagulation time following BI 11634 5 mg to 25 mg IR-tablets in the range of 1.98 to 2.85. It correlated with the squared root of BI 11634 plasma concentration ($R^2 = 0.90$). In contrast, aPTT, PRT, and PT-INR appeared insensitive to plasma BI 11634 concentrations. *Inhibition of endogenous factor Xa:* RVV reached 61.8% to 93.4% for the dose range of 5 mg to 25 mg BI 11634. The PK/PD relationship was best described by a sigmoid I-max model. The mean maximum inhibition of factor Xa activity as studied with COAMATIC© test ranged from 17.7% (5 mg) to 41.5% (25 mg). *Endogenous thrombin related biomarkers:* Mean maximum inhibition of ETP ranged between 11.7% (5 mg) and 31.3% (25 mg). Mean maximum peak inhibition of thrombin reached 46.5% to 85.1% and showed reasonable good correlation ($R^2 = 0.67$) with BI 11634 concentrations. Relative change in time to maximum thrombin inhibition varied from 1.44- to 2.02-fold; and prolongation of lag time of thrombin generation ranged from 1.40 to 2.01.
Safety results:	*Adverse events:* Overall 4/24 subjects experienced an AE: 1 subject (4.2%) reported an AE allocated to the screening period, 3/12 subjects (25%) developed AEs following 10 mg oral solution of BI 11634. No AEs were observed following 5 mg, 10 mg, and 25 mg BI 11634 as IR-tablet. The treatment-emergent AEs diarrhoea, fatigue, and occult faecal blood (one positive test) occurred in 1 subject each. All 3 treatment-emergent AEs were judged by the investigator as drug-related. None of the AEs was of severe intensity, none was leading to drug discontinuation and all were reported as resolved. The single occurrence of a positive test for occult faecal blood does not generate a significant safety signal. *Vital signs and ECG data:* Vital signs and ECG data did not demonstrate any consistent, treatment- or dose-related changes following BI 11634 administered as IR-tablet or drinking solution.

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Safety results (cont.):

Laboratory data:
Descriptive statistics of safety blood laboratory as well as analysis of transitions of individual data from 'normal' at baseline to 'abnormal' following treatment with BI 11634 did not indicate any specific pattern pointing towards clinically-relevant, treatment-induced, dose-related untoward reactions. Urinalysis was stated as normal in all subjects at all time points of assessment.

Global clinical assessment:
The global tolerability of BI 11634 was assessed as 'good' in all subjects.

Conclusions:

The IR-tablet formulation of BI 11634 as assessed following single oral doses of 10 mg was bioequivalent to the drinking solution with respect to $AUC_{0-\infty}$. C_{max}, however, was slightly greater for the IR-tablet than for the solution.

There was no evidence to conclude a deviation from dose proportionality between 5 mg and 10 mg of BI 11634 IR-formulation. However, dose proportionality could not be shown over the whole dose range of 5 mg to 25 mg for both $AUC_{0-\infty}$ and C_{max} data.

HepTest® was a sensitive coagulation test in terms of pharmacodynamic response range and correlation with BI 11634 plasma concentration. Moreover, inhibition of endogenous factor Xa activity by Russell's Viper Venom test appeared to be a sensitive biomarker for BI 11634. The inhibition of thrombin peak also showed reasonable good correlation ($R^2 = 0.67$) with plasma BI 11634 concentration and nearly full range of response in the studied doses.

In the dose range of 5 mg to 25 mg, BI 11634 following single oral doses was safe and well tolerated by 24 healthy male subjects irrespective of the formulation administered (IR-tablet or drinking solution).