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.:** 2007-001265-15	
Name of active ingredient: BI 11634		**Page:** 1 of 6	**Synopsis No.:**
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Report date: 14 AUG 2009	**Trial No. / U No.:** 1234.2 / U09-1833-01	**Date of trial:** 11 JUN 2007 – 14 SEP 2007	**Date of revision:** Not applicable

Title of trial:	Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple, rising oral doses of 2.5 mg, 5 mg, 7.5 mg, and 10 mg BI 11634 oral solution administered t.i.d. for 5 days to healthy male volunteers; randomised, double-blind, placebo-controlled at each dose level
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted], Germany
Publication (reference):	Data of this trial has not been published.
Clinical phase:	I
Objectives:	First evaluation of safety, tolerability, pharmacokinetics, and the pharmacodynamic effect of BI 11634 on coagulation parameters after multiple-dose administration (no primary endpoint in a statistical sense defined)
Methodology:	Randomised, double-blind, placebo-controlled at each dose level, rising multiple-dose, single-centre
No. of subjects:	
planned:	entered: 48 (12 subjects per dose group)
actual:	enrolled: 48 (12 subjects per dose group)
	Treatment BI 11634 oral solution: entered: 36 (9 subjects per dose group) treated: 36 analysed: 36
	Treatment BI 11634 placebo oral solution: entered: 12 (3 subjects per dose group) treated: 12 analysed: 12
Diagnosis and main criteria for inclusion:	Healthy male subjects were included provided they were ≥18 years and ≤50 years of age and had a BMI of ≥18.5 kg/m^2 and ≤29.9 kg/m^2.

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Test product:	BI 11634 powder for preparation of drinking solution (reconstituted solution: 200 mg BI 11634 powder diluted in 80 mL tartaric acid 0.5%)	
dose:	2.5 mg, 5 mg, 7.5 mg, and 10 mg (1 to 4 mL reconstituted solution diluted with water ad 160°mL plus 80 mL water to rinse the oropharyngeal mucosa)	
mode of admin.:	Oral administration for 5 consecutive days (Days 1 to 4 t.i.d., Day 5 once daily)	
batch no.:	BI 11634: B07100822	tartaric acid: B050404
Reference therapy:	Placebo to BI 11634 oral solution (reconstituted placebo solution: 40 mg placebo powder diluted in 80 mL tartaric acid 0.5%)	
dose:	1 to 4 mL reconstituted placebo solution diluted with water ad 160 mL plus 80°mL water to rinse the oropharyngeal mucosa	
mode of admin.:	Oral administration for 5 consecutive days (Day 1 to 4: t.i.d., Day 5: once daily)	
batch no.:	Placebo: B071000511	tartaric acid: B050404
Duration of treatment:	5 days (multiple-dose)	
Criteria for evaluation:		
Efficacy / clinical pharmacology:	Pharmacodynamics:	Coagulation tests including aPTT, PTR, PT-INR, HepTest®, anti-factor-Xa assays including COAMATIC© test and Russel's Viper Venom (RVV) test, endogenous thrombin potential (ETP) related parameters
	Pharmacokinetics:	Plasma concentration time profiles of BI 11634, pharmacokinetics (dose proportionality, terminal half life, renal excretion), attainment of steady state, accumulation ratios
Safety:	Physical examination, blood pressure (BP), pulse rate (PR), electrocardiogram (ECG), safety laboratory tests including faecal occult blood (FOB) tests, monitoring of adverse events (AEs) and assessment of global tolerability	
Statistical methods:	Descriptive statistics were calculated for safety, PK, and PD endpoints. Dose proportionality was explored using a regression model. To assess the attainment of steady state, trough concentrations (on the logarithmic scale) were analysed by a linear model with time as a repeated effect.	

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Pharmacokinetics:

Steady state was reached at about 48 h of treatment with BI 11634 oral solution. $C_{max,ss}$ and $AUC_{0-\tau,ss}$ generally increased in a dose-proportional manner for the dose range of 2.5 mg to 7.5 mg t.i.d, for 10 mg a less than proportional increase was observed. BI 11634 was rapidly absorbed with a median $t_{max,ss}$ of 0.5 h. After attainment of $C_{max,ss}$, plasma concentrations declined rapidly.

BI 11634 Treatment **Single dose Day 1**	$AUC_{0-\tau,1}$ [h.nmol/L] arithm. mean	CV%	C_{max} [nmol/L] arithm. mean	CV%	t_{max} [h] median	range	$CL_{R,0-8,1}$ [h] arithm. mean	CV%	fe_{0-24} [%] arithm. mean	CV%
2.5 mg	130	29.4	64	29.2	0.50	0.483-1.00	2.78	22.6	6.74	16.5
5 mg	240	20.9	112	22.6	0.50	0.483-1.03	2.48	24.4	5.94	17.7
7.5 mg	363	19.0	168	10.2	0.50	0.483-1.02	3.31	23.4	6.48	27.2
10 mg	424	24.3	199	30.0	0.50	0.500-0.51	2.76	29.1	4.67	20.0
Steady state Day 5	$AUC_{0-\tau,ss}$ [h.nmol/L] arithm. mean	CV%	$C_{max,ss}$ [nmol/L] arithm. mean	CV%	$t_{max,ss}$ [h] median	range	$CL_{R,0-8,ss}$ [h] arithm. mean	CV%	$t_{1/2,ss}$ [h] arithm. mean	CV%
2.5 mg	148	29.0	70	20.7	0.50	0.483-0.98	3.21	25.3	2.47	52.4
5 mg	284	24.1	130	25.6	0.50	0.483-1.02	2.74	26.8	3.47	79.3
7.5 mg	415	24.7	195	14.5	0.50	0.483-0.53	3.95	24.4	2.66	25.3
10 mg	470	24.1	212	20.1	0.52	0.500-1.00	3.77	25.6	3.13	57.4

The mean accumulation ratios based on AUC and C_{max} ranged between 1.11 and 1.19 indicating modest plasma accumulation after multiple dosing of 2.5 mg to 10 mg t.i.d. BI 11634 oral solution. The comparable steady state and single dose CL_R suggested that the oral clearance over the studied dose range did not depend on dose. At steady state, less than 10% of the administered dose were excreted in urine as unchanged drug.

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Clinical pharmacology results (cont.):

Pharmacodynamics:
HepTest®, RVV inhibition, and COAMATIC© test also at steady state were in overall good accordance with BI 11634 plasma concentrations, while the endogenous thrombin potential related biomarkers showed only poor correlation to BI 11634 plasma concentrations. RVV inhibition was the most sensitive biomarker to monitor the pharmacodynamic effects of BI 11634 at steady state.

Coagulation tests:
HepTest® ratio indicated a mean maximum prolongation of coagulation time following 2.5 mg to 10 mg t.i.d. BI 11634 in the range of 1.60 to 1.98. Heptest® ratio correlated well with the squared root of BI 11634 plasma concentration (R^2=0.90). There was no accumulation in Heptest® ratios following multiple dosing. Coagulation tests aPTT, PRT, and PT-INR appeared to be insensitive to plasma BI 11634 concentrations also at steady state.

Inhibition of endogenous factor Xa:
Over the studied dose range of 2.5 to 10 mg t.i.d. BI 11634, steady state RVV inhibition ranged from 37.9% (2.5 mg) to 82.9% (10 mg). RVV inhibition did not show an accumulation after multiple dosing. The PK/PD relationship was best described by a sigmoid E-max model with R^2= 0.95. The mean maximum inhibition of factor Xa activity as studied with COAMATIC© test ranged only from 10.4% (2.5 mg) to 27.1% (10 mg) at steady state and did not show an accumulation as compared to single-dose values.

Endogenous thrombin related biomarkers:
At steady state following 2.5 mg to 10 mg t.i.d. BI 11634, mean maximum inhibition of endogenous thrombin potential ranged from 20.7% to 27.3%, mean maximum peak inhibition of thrombin ranged from 50.7% to 67.6%; relative change in time to peak inhibition was 1.40- to 1.48-fold, and prolongation of lag time of thrombin generation was in the range of 1.39 to 1.55. All of these biomarkers showed poor correlation to BI 11634 plasma concentrations.

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Safety results:

Adverse events: Overall, 15/48 subjects (31.3%) experienced 20 AEs: 2 subjects developed AEs on placebo, 1 subject on BI 11634 2.5 mg t.i.d., 2 subjects on BI 11634 5 mg t.i.d., 4 subjects on BI 11634 7.5 mg t.i.d., and 4 subjects on BI 11634 10 mg t.i.d..

Moreover, 1 subject experienced an AE in a post-treatment phase (3 days after last dosing of BI 11634 5 mg t.i.d.) and 1 subject reported an SAE post-trial following placebo (knee effusion of moderate intensity, assessed as unrelated to trial medication, requiring hospitalisation for knee joint puncture).

The percentage of subjects experiencing drug-related AEs was the least on placebo (n = 1, 8.3%) and increased from the lowest to the highest dose group of BI 11634: 2.5 mg t.i.d. (n = 1, 11.1%), 5 mg t.i.d. (n = 2, 22.2%), 7.5 mg t.i.d. (n = 3, 33.3%), and 10 mg t.i.d. (n = 4, 44.4%).

The most frequent AEs (38.9%) were related to the gastrointestinal system (mainly diarrhoea, dyspepsia, flatulence, vomiting), followed by nervous system disorders (27.8%) (mainly headache, dizziness). Gastrointestinal disorders showed the highest incidence in the highest dose group (33.3%); no specific pattern was perceived. Fatigue occurred in 2 subjects each of the 7.5 mg and the 10 mg dose groups.

Two subjects experienced a positive faecal occult blood (FOB) test potentially related to the pharmacodynamic actions of BI 11634 (1 subject on 2.5 mg t.i.d., 1 subject on 7.5 mg t.i.d.). Single subjects with positive FOB tests had been observed in previous trials with BI 11634.

None of the reported AEs was of severe intensity, all events were reported as recovered at the end of the trial. No event led to drug discontinuation. Deaths were not observed, 1 subject experienced a SAE (see above, post-trial following placebo).

Vital signs: Vital signs did not demonstrate any consistent, treatment- or dose-related changes.

ECG data: Although some statistically significant changes in QTc intervals as compared with placebo and adjusted for baseline as a covariate were observed on a 10% significance level, absolute values were very small (maximum mean changes 7 ms) and did not indicate any dose-effect relation. Taken together, ECG data did not seem to suggest a clinically relevant effect of BI 11634 on QTc intervals.

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Safety results (cont.):

Laboratory data:
Descriptive statistics of safety blood laboratory and urinalysis 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.

Global clinical assessment:
The global tolerability of BI 11634 was assessed as 'good' in all subjects except for 1 subject in the 10 mg dose group (experiencing tiredness, flatulence, and dizziness) in whom it was assessed as 'satisfactory'.

Conclusions:

Steady state following multiple doses of 2.5 mg to 10 mg t.i.d. BI 11634 oral solution was reached at about 48 h of treatment. C_{max} and $AUC_{0-\tau}$ at steady state generally increased in a dose-proportional manner for the dose range of 2.5 mg to 7.5 mg t.i.d.; for 10 mg a less than proportional increase was observed. The mean terminal elimination half-lives ranged between 2.47 h and 3.47 h.

The t.i.d. dosage regimen resulted in a modest accumulation of BI 11634 plasma concentrations with accumulation ratios of 1.11 to 1.19. At steady state, less than 10% of the dose administered were excreted in urine as unchanged drug.

HepTest® ratio and inhibition of endogenous factor Xa activity as assessed by RVV test appeared to be sensitive biomarkers for BI 11634, whereas the endogenous thrombin related biomarkers showed poor correlation with BI 11634 plasma concentration. HepTest® ratio and RVV inhibition did not demonstrate an accumulation after multiple dosing.

Drug-related AEs (including gastrointestinal disorders and fatigue) tended to increase with the dose of BI 11634 administered. Overall, BI 11634 was safe and adequately well tolerated by 48 healthy male subjects following multiple doses of 2.5 mg to 10 mg t.i.d. oral solution.