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.:** 2007-003283-21	
Name of active ingredient: BI 11634		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 19 DEC 2008	**Trial No. / U No.:** 1234.7 / U08-2284-01	**Dates of trial:** 22 OCT 2007 – 12 DEC 2007	**Date of revision:** Not applicable

Title of trial:	An open, randomised, single-dose, four-way cross-over formulation-finding study of the oral bioavailability of four prototype extended-release formulations with 25 mg BI 11634, and intra-individual comparison to immediate-release tablets (25 mg) in healthy male volunteers
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre, Ingelheim am Rhein, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	To compare the oral bioavailability and rate of absorption of four prototype extended-release (ER) formulations with 25mg[1] BI 11634 (single doses) to immediate-release (IR) tablets in healthy male volunteers.
Methodology:	Open-label, single-dose treatment with IR-tablets 25 mg BI 11634, followed by a randomised, four-way cross-over of single-dose treatments with four prototype ER-formulations with 25[1] mg BI 11634, respecting a wash-out of at least 5 days between subsequent treatments.
No. of subjects:	
planned:	entered: 16 subjects
actual:	enrolled: 17 subjects Treatment I: BI 11634 IR-tablet 25 mg: entered: 17 treated: 17 analysed (for primary endpoint): 17 Treatment A: BI 11634 ER-tablet 25 mg (Formulation A): entered: 17 treated: 14 analysed (for primary endpoint): 14 Treatment B: BI 11634 ER-tablet 25 mg (Formulation B): entered: 17 treated: 15 analysed (for primary endpoint): 15

[1] for one formulation ('M'), the dose was 28 mg for technical reasons

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No. of subjects: **actual (cont.):**	Treatment C: BI 11634 ER-capsule 25 mg (Formulation C): entered: 17 treated: 15 analysed (for primary endpoint): 15 Treatment M: BI 11634 ER-capsule 28 mg (Formulation M): entered: 17 treated: 14 analysed (for primary endpoint): 14
Diagnosis and main criteria for inclusion:	Healthy male subjects were included provided they were between 21 and 45 years of age and had a BMI of ≥18.5 and ≤29.9 kg/m^2.
Test product:	BI 11634 ER-tablets 25 mg (Formulation A) = fast-release ER matrix tablet BI 11634 ER-tablets 25 mg (Formulation B) = slow-release ER matrix tablet BI 11634 ER-capsules 25 mg (Formulation C) = slow-release ER-capsule (filled with matrix mini-tablets) BI 11634 ER-capsules 28 mg (Formulation M) = slow-release ER-capsule (filled with extrusion pellets)
dose:	25 mg (Formulation M: 28 mg due to technical reasons)
mode of admin.:	Oral administration after an overnight fast with 240 mL water
batch no.:	Ch.-B No.: B071001948 (Formulation A), B071002066 (Formulation B), B071002465 (Formulation M), B071002290 (Formulation C)
Reference therapy:	BI 11634 IR-tablet (Formulation I)
dose:	25 mg
mode of admin.:	Oral administration after an overnight fast with 240 mL water
batch no.:	Ch.-B No.: B071001877
Duration of treatment:	One day (single oral dose) for each treatment
Criteria for evaluation:	
Clinical pharmacology:	Pharmacodynamics: HepTest®, RVV (Russel's Viper Venom) test 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, C_{max}/C_{24}
Safety:	Physical examination, vital signs (blood pressure (BP); pulse rate (PR)), ECG, laboratory tests including tests for faecal occult blood (FOB), monitoring for adverse events (AE), and assessment of global tolerability

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Statistical methods:

Each ER-formulation was separately compared with the IR-tablet. Point estimates (geometric means) of the median intra-subject ratios of $AUC_{0-\infty}$ and C_{max} and their two-sided 90% confidence intervals (CIs) were calculated.

The statistical model applied to analyse bioavailability was an ANOVA on the logarithmic scale including effects for 'subjects' and 'treatment'. CIs were based on the residual error from ANOVA in the respective paired comparisons. All other parameters were summarised by descriptive statistics.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

The 17 healthy male subjects participating in this trial were 33.9± 4.2 years old and had a BMI of 25.3± 2.6 kg/m^2 (mean± SD).

Pharmacokinetics: Mean AUC_{0-tz} and $AUC_{0-\infty}$ of the ER-formulations were about 38% to 70% of the values observed for the IR-tablet, while $t_{1/2}$ of ER-formulations were clearly increased, suggesting all ER-formulations showed controlled-release properties. The mean MRT_{po} was substantially prolonged for all ER-formulations compared with the IR-tablet (maximum 11.4 h with Formulation A):

	Treatment				
	I **IR-tablet** n=17	**A** **ER-tablet** n=14	**B** **ER-tablet** n=15	**C** **ER-capsule** n=15	**M** **ER-capsule** n=14
	arithm. mean	arithm. mean	arithm. mean	arithm. mean	arithm. mean
$AUC_{0-\infty}$ [h*nmol/L]	1340	727	773	528	941
AUC_{0-tz} [h*nmol/L]	1320	654	712	496	896
C_{max} [nmol/L]	463	82.0	89.4	76.7	159
$t_{1/2}$ [h]	1.84	8.60	6.29	6.37	7.99
MRT_{po} [h]	3.15	11.4	9.99	8.84	8.35
CL/F [L/h]	44.8	86.3	80.2	121	74.0
C_{max}/C_{24}	-	14.0[a]	12.9[b]	21.8[c]	28.9[d]
	Median	Median	Median	Median	Median
t_{max} [h]	0.983	1.76	3.93	3.95	1.95

[a] n =12, [b] n =14, [c] n =10, [d] n =11

Relative bioavailability: The relative bioavailability of the ER-formulations vs. the IR-tablet based on $AUC_{0-\infty}$ was 52.1% (90% CI: 46.6%-58.2%), 55.5% (90% CI: 50.3%-61.2%), 37.5% (90% CI: 33.3%-42.3%), and 60.6% (90% CI: 53.0 %-69.2 %) for Formulations A, B, C, and M, respectively.

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Clinical pharmacology results (cont.):

Coagulation times as assessed by HepTest®: The mean E_{max} values for HepTest® were 27.5 s, 28.4 s, 27.6 s, and 32.8 s, after administration of Formulations A, B, C, and M, respectively. The Heptest® ratios at 16 h post dose were 1.19, 1.17, 1.13, and 1.14 for Formulations A, B, C, and M, respectively, indicating an anticoagulation effect for all ER-formulations. At 24 h post dose, the Heptest® ratios were 1.15, 1.13, 1.09, and 1.06, respectively, suggesting persistence of anticoagulation for Formulations A and B.

Inhibition of endogenous Factor Xa as assessed by RVV inhibition: The mean E_{max} values for RVV inhibition were 45.7%, 46.9%, 39.9%, and 66.5% for Formulations A, B, C, and M, respectively. Later than 8 h after dosing, this biomarker did not consistently indicate pharmacodynamic effects.

Pharmacodynamic-kinetic relationship: The mean pattern of the pharmacodynamic effect exerted by BI 11634 as assessed by HepTest® and RVV inhibition was generally in accordance with plasma BI 11634 concentrations. Pharmacokinetic and -dynamic t_{max} values were almost matched to each other (except for RVV inhibition Formulation A). HepTest® ratios correlated well with the square root of BI 11634 plasma concentrations, while the PK/PD relationship of RVV inhibition can be best described by a sigmoid E_{max} model.

Safety results

A total of 13 subjects received all 5 formulations, 1 subject received 4 (I,A,M,C), 1 subject 3 (I,B,C), 1 subject 2 (I,B), and 1 subject 1 formulation(s) (I). Thus, the total cumulative dose of BI 11634 by subject ranged from 25 mg to 128 mg.

Adverse events: Overall, 9 subjects experienced a total of 16 AEs. Three subjects reported AEs not allocated to a treatment period. Treatment-emergent AEs were observed in 5/17 subjects (29.4%) following administration of the IR-tablet, 1/14 subjects (7.1%) following administration of Formulation A, 4/15 subjects (26.7%) following administration of Formulation B, 1/15 subjects (6.7%) following administration of Formulation C, and 1/14 subjects (7.1%) following administration of Formulation M. Thus, the IR-tablet and Formulation B were associated with a higher incidence of AEs than the other formulations; mainly headache not considered related to the study medication was reported with both formulations alike.

Only 1 AE was assessed by the investigator as related to study medication (positive FOB test of mild intensity following the IR-tablet). None of the AEs was of severe intensity. All AEs were reported as resolved at the end of the observation period or were adequately followed up. Deaths or other serious AEs were not observed.

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Safety results (cont.):

Adverse events (cont.): Regarding all treatments with BI 11634, the most frequent AE observed was headache: 9 events were reported by 5 subjects. Two subjects developed haematoma following the administration of the IR-tablet. Both events were considered not related to the study medication; in one subject moderate haematoma was most likely caused by the performance of sports, in the other subject mild haematoma was related to the insertion of a venous cannula.

Overall 2 subjects discontinued the trial prematurely due to AEs (n=1 ulnar fraction not related to study medication, n=1 positive FOB test). The single occurrence of a (potentially) drug-related positive FOB test in a subject with 2nd degree haemorrhoids does not generate a significant safety signal.

Vital signs and ECG data: Vital signs and ECG data did not demonstrate any consistent, treatment-related changes following BI 11634 administered as IR-tablet or ER-formulations.

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 demonstrate any specific pattern indicating clinically relevant, treatment-induced or formulation-related untoward reactions. Prolongations in coagulation time assessed by HepTest® at 3 h after dosing of all 5 formulations reflected the pharmacodynamic effects of BI 11634. None of the occasionally observed abnormal findings in urinalysis indicated a significant safety signal.

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

Conclusions:

Formulations A and B out of the 4 ER-prototypes under investigation demonstrated prolonged plasma half-life as compared with the IR-tablet and persistent anticoagulation effects at 16 hours and 24 hours after drug administration combined with an adequate relative bioavailability.

BI 11634 administered in single oral doses of 25 mg (1 IR- and 3 ER-formulations) and 28 mg (the 4th ER-formulation) was safe and well tolerated.