Boehringer Ingelheim

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.

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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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-018088-29	
Name of active ingredient: BI 10773		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 30 NOV 2010	**Trial No. / U No.:** 1245.18 / U10-2984-01	**Dates of trial:** 17 MAY 2010 – 07 JUL 2010	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of both BI 10773 and warfarin and pharmacodynamics of warfarin after co-administration compared to multiple oral doses of BI 10773 (25 mg once daily) and a single oral dose of warfarin (25 mg) alone in healthy male volunteers (an open-label, crossover, clinical phase I study)
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Clinical Research/Human Pharmacology Centre, Biberach, Germany
Publication (reference):	Data of this trial have not been published
Clinical phase:	I
Objectives:	The objective of this trial was to study the bioavailability of BI 10773 and warfarin when giving multiple doses of BI 10773 together with a single dose of warfarin compared to their bioavailability when giving BI 10773 or warfarin alone. Furthermore, the pharmacodynamics of a single dose of warfarin with and without concomitant multiple doses of BI 10773 were investigated.
Methodology:	This was an open-label, crossover study with 3 treatments (A, B, and C) and 2 treatment sequences (AB_C and C_AB).
No. of subjects:	
planned:	entered: 18 total (9 in each of the 2 treatment sequences)
actual:	entered: 18 Treatment A (BI 10773): treated and analysed (for primary endpoint): 18 Treatment B (BI 10773 + warfarin): treated and analysed (for primary endpoint): 18 Treatment C (warfarin): treated and analysed (for primary endpoint): 18
Diagnosis and main criteria for inclusion:	Healthy male subjects at the age of 18 to 55 years with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 and with a homozygote wild-type allele (*1/*1) of CYP2C9 were included.

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Test product 1:	BI 10773 tablets
dose:	25 mg once daily
mode of admin.:	Oral
batch no.:	909473A
Test product 2:	Warfarin (Coumadin®) tablets
dose:	25 mg single dose
mode of admin.:	Oral
batch no.:	9K23 (Bristol-Myers Squibb GmbH & Co. KGaA)
Duration of treatment:	Treatment A (5 days): BI 10773 was given once daily on Days 1 to 5 Treatment B (8 days): BI 10773 was given once daily on Days 1 to 7 and warfarin was given as a single dose on Day 1 Treatment C (8 days): warfarin was given as a single dose on Day 1 BI 10773 was given continuously from Day 1 of Treatment A to Day 7 of Treatment B, ensuring steady state conditions of BI 10773 on the day of warfarin co-administration on Day 1 of Treatment B. A washout period of at least 14 days was required between drug administrations in treatments B and C (sequence AB_C) and between drug administrations in treatments C and A (sequence C_AB).
Criteria for evaluation:	
Clinical pharmacology:	The following pharmacokinetic parameters were analysed as primary endpoints: $AUC_{\tau,ss}$ and $C_{max,ss}$ for BI 10773 and $AUC_{0-\infty}$ and C_{max} for warfarin (determined separately for the *R*- and *S*-enantiomers). The following pharmacokinetic parameters were assessed as secondary endpoints: $C_{24,N}$, $t_{max,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$ for BI 10773 and $AUC_{0-tz,}$ t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F for warfarin (determined separately for the *R*- and *S*-enantiomers).

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Clinical pharmacology (continued):	The following pharmacodynamic parameters were assessed as secondary endpoints for warfarin: INR_{max} (peak international normalised ratio), INR $AUEC_{0-tz}$, $INR_{max,base}$, INR $AUEC_{0-tz,base}$, PT_{max} (peak prothrombin time), PT $AUEC_{0-tz}$, $PT_{max,base}$, and PT $AUEC_{0-tz,base}$
Safety:	The evaluation of safety as a secondary endpoint was based on physical examination, monitoring of vital signs (blood pressure [BP] and pulse rate [PR]), 12-lead electrocardiogram (ECG), clinical laboratory tests (clinical chemistry, urinalysis, and haematology as well as determination of prothrombin time [PT] and international normalised ratio [INR]), monitoring of adverse events, and assessment of overall tolerability.
Statistical methods:	Descriptive statistics were calculated for all pharmacokinetic, pharmacodynamic and safety endpoints. Point estimators (geometric means) of the median intrasubject ratios of $AUC_{\tau,ss}$ and $C_{max,ss}$ (for BI 10773) and of $AUC_{0-\infty}$ and C_{max} (for warfarin) and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model used to determine the relative bioavailability of BI 10773 (treatments A and B) was an analysis of variance (ANOVA) model on the logarithmic scale, with terms for 'subject' and 'treatment'. The model used to determine the relative bioavailability of warfarin (treatments B and C) was an ANOVA model on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. Confidence intervals were based on the residual error from the ANOVA. The pharmacodynamic endpoints INR $AUEC_{0-tz}$, INR_{max}, INR $AUEC_{0-tz,base}$, $INR_{max,base}$, PT $AUEC_{0-tz}$, PT_{max}, PT $AUEC_{0-tz,,base}$, $PT_{max,base}$ were evaluated using an ANOVA including 'sequence', 'subjects within sequences', 'period', and 'treatment' as effects and the respective baseline value of INR or PT as a covariate. Two-sided 95% CIs were calculated. Attainment of steady state of BI 10773 was analysed by a repeated measures ANOVA including 'subject' and 'time' as effects.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:	All 18 entered subjects completed the trial according to the clinical trial protocol. The trial population consisted of healthy white male subjects. The mean age was 34.8 years, ranging from 21 to 46 years, and the mean BMI was 25.0 kg/m^2, ranging from 19.5 to 29.4 kg/m^2.

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Clinical pharmacology results (continued):

Mean plasma concentration-time profiles of BI 10773 at steady state were not influenced by the presence and absence of a single dose of warfarin ($AUC_{\tau,ss}$: 4670 nmol·h/L for combined treatment compared with 4620 nmol·h/L for BI 10773 alone; $C_{max,ss}$: 785 nmol/L compared with 774 nmol/L; $t_{max,ss}$: 1.47 h compared with 1.44 h). Likewise, mean plasma concentration-time profiles of *R*-warfarin were similar when given in combination with steady state BI 10773 or alone ($AUC_{0-\infty}$: 64400 ng·h/mL for combined treatment compared with 64900 ng·h/mL for warfarin alone; C_{max}: 1390 ng/mL compared with 1420 ng/mL; t_{max}: 1.54 h compared with 1.27 h). This was also true for *S*-warfarin ($AUC_{0-\infty}$: 36400 ng·h/mL for combined treatment compared with 38100 ng·h/mL for warfarin alone; C_{max}: 1440 ng/mL compared with 1460 ng/mL; t_{max}: 1.25 h compared with 1.17 h). Exposure, oral clearance and volume of distribution of BI 10773 and of *R*- and *S*-warfarin were similar for each substance when given alone or in combination.

The adjusted gMean ratios and 90% CIs of $AUC_{\tau,ss}$ and $C_{max,ss}$ for BI 10773 and $AUC_{0-\infty}$ and C_{max} for *R*- and *S*-warfarin are summarised in Table 1.

Table 1 Relative bioavailabilities of BI 10773 and warfarin when given concomitantly (test treatment) and when given alone (reference treatment)

Analyte/ Parameter	Test treatment N=18	Reference treatment N=18	gMean ratio of test to reference treatment [%]	90% CIs of gMean ratio [%]
BI 10773				
$AUC_{\tau,ss}$	BI 10773 + warfarin	BI 10773	100.89	96.86, 105.10
$C_{max,ss}$	BI 10773 + warfarin	BI 10773	100.64	89.79, 112.80
R-warfarin				
$AUC_{0-\infty}$	BI 10773 + warfarin	Warfarin	98.49	95.29, 101.80
C_{max}	BI 10773 + warfarin	Warfarin	97.89	91.12, 105.15
S-warfarin				
$AUC_{0-\infty}$	BI 10773 + warfarin	Warfarin	95.88	93.40, 98.43
C_{max}	BI 10773 + warfarin	Warfarin	98.88	91.84, 106.47

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Clinical pharmacology results (continued):

Applying the standard bioequivalence criteria of 80 to 125%, the results show that co-administration of BI 10773 and warfarin did not affect either the extent or the rate of absorption of BI 10773, *R*-warfarin, or *S*-warfarin. Intraindividual variability was generally low for both BI 10773 and warfarin treatments. The geometric coefficients of variation [gCV] for the AUC values of BI 10773, *R*-warfarin, and *S*-warfarin were 7.0%, 5.7%, and 4.5%, respectively; gCVs for C_{max} of the 3 analytes were 19.9%, 12.4%, and 12.7%, respectively.

Co-administration of BI 10773 with warfarin did not significantly alter effects of warfarin on PT and INR. The gMean ratios and 95% CIs are presented in Table 2.

Table 2 Summary of pharmacodynamic parameters of warfarin administered alone or in combination with BI 10773

Parameter	Warfarin alone		Warfarin + BI 10773		gMean ratio of BI 10773 + warfarin to warfarin (95% CIs)
	N	gMean	N	gMean	
PT_{max} [s]	16	20.2	16	18.1	0.90 (0.79, 1.02)
PT $AUEC_{0-168}$ [s*h]	10	2508	15	2282	0.91 (0.84, 0.98)
INR_{max}	16	1.76	16	1.53	0.87 (0.73, 1.04)
INR $AUEC_{0-168}$	10	203	15	178	0.88 (0.79, 0.98)

Safety results:

Each of the 18 treated subjects received a total dose of 300 mg BI 10773 (25 mg once daily) and a total dose of 50 mg warfarin (two 25mg single doses) during the course of the trial as planned.

In this trial, a total of 9 subjects (50.0%) reported at least 1 adverse event during 1 of the 3 treatments. Four subjects (22.2%) experienced an adverse event while taking BI 10773 alone, 2 subjects (11.1%) during treatment with BI 10773 and warfarin, and 5 subjects (27.8%) while taking warfarin alone.

Headache was the most frequently reported adverse event (22.2% overall). It was experienced by 3 subjects (16.7%) during treatment with BI 10773 alone, by 2 subjects (11.1%) during treatment with warfarin alone, and by none during the combined treatment. All other adverse events were only reported by 1 subject each. One adverse event was judged as drug-related by the investigator. This concerned 1 case of mild petechiae, which was reported by 1 subject following treatment with warfarin alone.

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Safety results (continued):

All adverse events were of mild or moderate intensity. No serious adverse events and no adverse events leading to discontinuation of trial medication were reported in this trial. One subject received concomitant medication because of his adverse event and all subjects recovered from their adverse events.

The global tolerability assessment was 'good' for all subjects for all treatments. Furthermore, there were no clinically relevant findings with respect to the clinical laboratory evaluation, vital signs, and ECG recordings.

Conclusions:

Warfarin co-administration had no clinically relevant effect on either the extent or rate of absorption of BI 10773, as determined by the standard bioequivalence boundaries. Similarly, BI 10773 co-administration had no clinically relevant effect on either the extent or rate of absorption of warfarin and did not significantly alter the effects of warfarin on PT or INR. These results demonstrate that there is no drug-drug interaction between BI 10773 and warfarin. No dosage adjustment of warfarin is required when warfarin and BI 10773 are prescribed concomitantly.

Furthermore, multiple daily doses of 25 mg BI 10773 and a single 25 mg dose of warfarin were well tolerated by healthy male subjects when given either alone or in combination.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for secondary endpoints of the trial. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
Comparison of PK Endpoints for BI 10773 after administration of BI 10773 with and without Warfarin	Table 15.6.3: 1
Comparison of PK Endpoints for R-Warfarin after administration of Warfarin with and without BI 10773	Table 15.6.3: 2
Comparison of PK Endpoints for S-Warfarin after administration of Warfarin with and without BI 10773	Table 15.6.3: 3

Table 15.6.3: 1 Comparison of pharmacokinetic parameters (N, gMean, gCV [%], Mean and CV [%]) of BI 10773 in plasma after multiple oral administration of 25 mg BI 10773 tablet qd with and without single dose of 25 mg Warfarin tablet qd treatment

	25 mg BI 10773					25 mg BI 10773 and 25 mg Warfarin				
	N	gMean	gCV [%]	Mean	CV [%]	N	gMean	gCV [%]	Mean	CV [%]
$AUC_{\tau,ss}$ [nmol*h/L]	18	4580	13.1	4620	13.0	18	4620	15.1	4670	15.5
$C_{max,ss}$ [nmol/L]	18	760	20.2	774	19.2	18	765	24.2	785	23.0
$t_{max,ss}$ [h]	18	1.36	35.0	1.44	39.2	18	1.24	55.5	1.47	83.2
$t_{½,ss}$ [h]	18	6.67	10.6	6.71	10.8	18	7.07	11.7	7.12	11.9
$\lambda_{z,ss}$ [1/h]	18	0.104	10.6	0.104	10.5	18	0.0980	11.7	0.0986	11.5
$CL/F_{,ss}$[mL/min]	18	187	14.8	189	14.8	18	183	16.9	185	16.2
$V_z/F_{,ss}$[L]	18	108	8.63	108	8.31	18	112	12.7	113	13.2
$MRT_{po,ss}$ [h]	18	8.64	12.6	8.71	12.4	18	9.08	17.5	9.21	18.1
$C_{pre,3}$ [nmol/L]	18	42.3	29.3	43.9	26.3	0	---	---	---	---
$C_{pre,4}$ [nmol/L]	18	42.7	31.5	44.5	28.1	0	---	---	---	---
$C_{pre,5}$ [nmol/L]	18	40.8	33.4	42.9	32.9	0	---	---	---	---
$C_{pre,6}$ [nmol/L]	0	---	---	---	---	18	37.2	32.1	38.9	29.8
$C_{pre,7}$ [nmol/L]	0	---	---	---	---	18	41.6	36.7	44.2	37.6
$C_{pre,8}$ [nmol/L]	0	---	---	---	---	18	39.3	31.3	41.1	31.7
$C_{pre,9}$ [nmol/L]	0	---	---	---	---	18	37.9	31.9	39.7	31.8
$C_{pre,10}$ [nmol/L]	0	---	---	---	---	18	43.9	33.6	46.3	38.3
$C_{pre,11}$ [nmol/L]	0	---	---	---	---	18	43.6	32.4	45.7	32.5
$C_{pre,12}$ [nmol/L]	0	---	---	---	---	18	44.6	41.7	48.3	44.6
$C_{pre,13}$ [nmol/L]	0	---	---	---	---	18	43.5	42.5	47.1	43.7

--- no descriptive statistics calculated
Cpre values are numbered according to scheduled dose

Source data: Section 15.6, Table 2.1: 1, 2.1: 2

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Table 15.6.3: 2 Comparison of pharmacokinetic parameters (N, gMean, gCV [%], Mean and CV [%]) of R-Warfarin in plasma after single oral administration of 25 mg Warfarin tablet qd with and without multiple doses of 25 mg BI 10773 tablet qd

	25 mg Warfarin					25 mg Warfarin and 25 mg BI 10773				
	N	gMean	gCV [%]	Mean	CV [%]	N	gMean	gCV [%]	Mean	CV [%]
AUC_{0-tz} [ng*h/mL]	18	58600	18.5	59500	18.9	18	57900	21.1	59100	21.3
$AUC_{0-\infty}$ [ng*h/mL]	18	63600	20.8	64900	21.2	18	62600	24.2	64400	24.5
C_{max} [ng/mL]	18	1400	14.4	1420	14.3	18	1370	17.9	1390	16.9
t_{max} [h]	18	0.998	79.5	1.27	78.7	18	1.06	98.7	1.54	115
$t_{½}$ [h]	18	47.1	12.1	47.5	12.0	18	45.8	15.4	46.3	15.1
λ_z [1/h]	18	0.0147	12.1	0.0148	12.1	18	0.0151	15.4	0.0153	15.5
CL/F [mL/min]	18	6.55	20.8	6.68	19.8	18	6.65	24.2	6.83	23.0
V_z/F [L]	18	26.7	15.5	27.0	15.1	18	26.4	13.6	26.6	13.7
MRT_{po} [h]	18	62.9	16.0	63.7	15.9	18	61.2	19.1	62.2	18.7

Source data: Section 15.6, Table 2.1: 3, 2.1: 4

Table 15.6.3: 3 Comparison of pharmacokinetic parameters (N, gMean, gCV [%], Mean and CV [%]) of S-Warfarin in plasma after single oral administration of 25 mg Warfarin tablet qd with and without multiple doses of 25 mg BI 10773 tablet qd

	25 mg Warfarin					25 mg Warfarin and 25 mg BI 10773				
	N	gMean	gCV [%]	Mean	CV [%]	N	gMean	gCV [%]	Mean	CV [%]
AUC_{0-tz} [ng*h/mL]	18	36400	17.4	36900	18.2	18	35000	15.4	35400	16.1
$AUC_{0-\infty}$ [ng*h/mL]	18	37500	17.8	38100	18.5	18	35900	16.1	36400	16.9
C_{max} [ng/mL]	18	1440	14.3	1460	14.2	18	1430	17.1	1440	16.3
t_{max} [h]	18	0.929	74.6	1.17	80.9	18	0.861	85.6	1.25	140
$t_{½}$ [h]	18	37.0	13.7	37.3	13.6	18	36.7	12.4	36.9	12.0
λ_z [1/h]	18	0.0187	13.7	0.0189	13.9	18	0.0189	12.4	0.0190	12.8
CL/F [mL/min]	18	11.1	17.8	11.3	17.1	18	11.6	16.1	11.7	15.3
V_z/F [L]	18	35.6	21.1	36.3	20.7	18	36.8	12.7	37.1	12.9
MRT_{po} [h]	18	40.8	13.8	41.2	13.1	18	38.9	15.0	39.3	14.5