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.:** 2009-011910-35	
Name of active ingredient: BIBW 2992		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 26 MAR 2010	**Trial No. / U No.:** 1200.80 / U10-1164-01	**Dates of trial:** 19 AUG 2009 – 05 OCT 2009	**Date of revision:** Not applicable

Title of trial:	Pharmacokinetics, safety and tolerability of BIBW 2992 administered orally as 20 mg, 30 mg, 40 mg, and 50 mg tablets (final formulation) to healthy male volunteers in an open-label, single rising dose, Phase I trial
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, Biberach, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The objectives were to assess the pharmacokinetic profiles and dose proportionality as well as safety and tolerability of 4 different dose strengths (20 mg, 30 mg, 40 mg, 50 mg) of BIBW 2992 final formulation tablets administered as single doses to healthy male volunteers.
Methodology:	The study was conducted as a single rising dose, open-label, inter-individual comparison study.
No. of subjects:	
planned:	entered: 48 (12 per dose group)
actual:	entered: 48
	BIBW 2992 20 mg: entered: 12 treated: 12 analysed (for primary endpoints): 12
	BIBW 2992 30 mg: entered: 12 treated: 12 analysed (for primary endpoints): 12
	BIBW 2992 40 mg: entered: 12 treated: 12 analysed (for primary endpoints): 11
	BIBW 2992 50 mg: entered: 12 treated: 12 analysed (for primary endpoints): 12
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 to 55 years, body mass index 18.5 to 29.9 kg/m^2

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Test product:	BIBW 2992 MA2 20 mg, 30 mg, 40 mg, 50 mg tablets (final formulation)
dose:	20 mg, 30 mg, 40 mg, 50 mg given as single doses
mode of admin.:	Oral administration with 240 mL water after an overnight fast
batch no.:	B071003953 (20 mg), B071003954 (30 mg), B071003957 (40 mg), B081000220 (50 mg)
Duration of treatment:	A single dose was administered to each subject followed by pharmacokinetic blood sampling for 120 h.
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic parameters of BIBW 2992: Primary endpoints: C_{max}, AUC_{0-tz}, $AUC_{0-\infty}$ Secondary endpoints: $\%AUC_{tz-\infty}$, AUC_{0-24}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F
Safety:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, analysis of adverse events (AEs), and global tolerability assessment. The severity of the AEs was assessed according to the 'Common Terminology Criteria for Adverse Events' (CTCAE Version 3.0).
Statistical methods:	Dose proportionality of the primary endpoints C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ of BIBW 2992 was explored using a log-transformed power model. From the resulting linear regression model, the point estimate of the slope β and its 2-sided 95% confidence interval (CI) were computed for each primary parameter. For all other pharmacokinetic parameters, descriptive statistics were calculated. Plots of plasma concentrations versus time were generated. The analysis of safety data was based on descriptive statistics.
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	A total of 48 healthy subjects were entered into 4 dose groups of 12 subjects each. All subjects completed the trial according to protocol. All subjects were white men and the mean age was 37.6 years. The dose groups were comparable with respect to demographic characteristics. No relevant concomitant medical conditions and concomitant therapies were reported. One subject in the 40 mg dose group had no measurable BIBW 2992 plasma concentrations und thus was not included in the calculation of pharmacokinetic parameters.

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Clinical pharmacology results (continued):

At all dose levels, the absorption of BIBW 2992 was moderately fast, reaching maximum plasma concentrations at a median t_{max} of 5.00 h after drug administration. The plasma concentration-time profiles were similarly shaped for all dose groups. BIBW 2992 plasma concentrations showed a moderate to high inter-subject variability with geometric coefficient of variation (gCV) values ranging between 23.5% and 216% per sampling timepoint.

The main pharmacokinetic parameters of BIBW 2992 (geometric mean [gMean] and gCV values) are summarised in the following table. For t_{max}, the median and range are given.

BIBW 2992 dose	20 mg N=12	30 mg N=12	40 mg N=11	50 mg N=12
	gMean (gCV%)	gMean (gCV%)	gMean (gCV%)	gMean (gCV%)
C_{max} [ng/mL]	7.78 (42.3)	13.7 (44.7)	24.3 (33.1)	37.1 (37.4)
AUC_{0-tz} [ng·h/mL]	179 (36.2)	308 (36.0)	526 (32.3)	697 (48.4)
$AUC_{0-\infty}$ [ng·h/mL]	189 (35.1)	327 (35.5)	549 (32.1)	724 (48.7)
t_{max} [h]	5.00 (2.00-8.00)	5.00 (1.00-6.00)	5.00 (5.00-6.00)	5.00 (4.00-5.00)
$t_{1/2}$ [h]	30.7 (10.6)	32.9 (24.8)	29.6 (12.6)	28.5 (15.5)
CL/F [mL/min]	1770 (35.1)	1530 (35.5)	1210 (32.1)	1150 (48.7)
V_z/F [L]	4700 (43.9)	4350 (42.7)	3110 (39.1)	2840 (54.8)

The primary pharmacokinetic parameters C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ increased over-proportionally with dose. The point estimates of the slope parameter β were 1.7134 (95% CI 1.3920, 2.0347), 1.5162 (95% CI 1.2036, 1.8288), and 1.4975 (95% CI 1.1879, 1.8071) for C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$, respectively. The inter-subject variability of the parameters C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ was comparable between the different dose groups, with gCV values ranging between 32.1% and 48.7%.

The gMean terminal half-life ($t_{1/2}$) ranged between 28.5 h and 32.9 h. A high apparent total body clearance (CL/F) and a high apparent volume of distribution (V_z/F) were observed that both decreased with increasing dose.

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Safety results:

Each subject was administered a single dose of BIBW 2992 either as 20 mg, 30 mg, 40 mg, or 50 mg tablet as planned.

No deaths, no serious AEs, and no AEs that led to discontinuation occurred during the trial. Nine out of 48 subjects (18.8%) reported at least 1 AE. Of these, 1 subject experienced an AE during screening, 2 subjects experienced AEs in the 20 mg dose group (headache: 1 subject, back pain: 1 subject), 3 subjects in the 30 mg dose group (headache: 2 subjects, epistaxis and diarrhoea: 1 subject), 1 subject in the 40 mg dose group (headache), and 2 subjects in the 50 mg dose group (diarrhoea: 1 subject, flatulence: 1 subject).

Four AEs were assessed as possibly drug-related by the investigator: diarrhoea in the 30 mg and 50 mg dose groups, epistaxis in the 30 mg dose group, and headache in the 40 mg dose group.

All AEs were of mild intensity (CTCAE grade 1) with the exception of back pain, which was rated as severe (CTCAE grade 3). Back pain, which was not considered drug-related, was the only AE that required treatment. All AEs had resolved completely by the end of the trial.

There were no notable findings with respect to the clinical laboratory evaluation, vital signs, and ECG recordings. Global tolerability was assessed as good for all 48 subjects.

Conclusions:

In the dose range investigated (20 mg to 50 mg), BIBW 2992 exhibited non-linear pharmacokinetics with an over-proportional increase in C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ (slope parameter β = 1.7134, 1.5162, and 1.4975, respectively).

Single doses of 20 mg, 30 mg, 40 mg, and 50 mg BIBW 2992 were well tolerated by healthy male volunteers. There were no notable differences between the dose groups with respect to safety and tolerability.