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.:** 2009-011909-16	
Name of active ingredient: BIBW 2992 / ritonavir		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 02 JUN 2010	**Trial No. / U No.:** 1200.79 / U10-1163-01	**Dates of trial:** 17 SEP 2009 – 14 DEC 2009	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of a single oral dose of BIBW 2992 (20 mg) after coadministration with multiple oral doses of ritonavir (200 mg bid for 3 days) compared to the bioavailability of a single oral dose of BIBW 2992 (20 mg) alone in healthy male volunteers (an open-label, randomised, two-way crossover, clinical phase I study)
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
Objective:	The objective was to investigate the effect of ritonavir, an inhibitor of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4), on the pharmacokinetics of BIBW 2992.
Methodology:	This was an open-label, randomised, 2-way crossover study with single-dose administration of BIBW 2992 and multiple-dose administration of ritonavir. Each subject underwent 2 treatment periods separated by a wash-out period.
No. of subjects:	
planned:	entered: 22
actual:	entered: 22 BIBW 2992 and ritonavir: treated: 22 analysed (for primary endpoints): 22 BIBW 2992 alone: treated: 22 analysed (for primary endpoints): 22
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥21 and ≤55 years, body mass index ≥18.5 and ≤29.9 kg/m^2

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Investigational product 1:	BIBW 2992 20 mg tablet
dose:	20 mg (single dose)
mode of admin.:	Oral
batch no.:	B071003953
Investigational product 2:	Ritonavir 100 mg capsule (Norvir®)
dose:	200 mg twice daily
mode of admin.:	Oral
batch no.:	72660VA (Abbott Laboratories Ltd.)
Duration of treatment:	Test treatment: 3 consecutive days of treatment with 200 mg ritonavir twice daily combined with a single oral dose of 20 mg BIBW 2992 in the morning of the second day. Reference treatment: single oral dose of 20 mg BIBW 2992 alone. The 2 BIBW 2992 administrations were separated by a wash-out period of at least 21 days.
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic parameters of BIBW 2992: Primary endpoints: $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} Secondary endpoints: AUC_{0-24}, $\%AUC_{tz-\infty}$, 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
Statistical methods:	$AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} were log-transformed prior to fitting an analysis of variance (ANOVA) model including effects for 'treatment', 'period', 'sequence', and 'subjects nested within sequence'. For the primary endpoints, 90% confidence intervals (CI) were computed, then back-transformed to the original scale to give the geometric mean (gMean) and interval estimates for the median test/reference ratio. For all other parameters, descriptive statistics are presented.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Twenty-two healthy male subjects were entered and treated in this trial. The mean age of the subjects was 38.2 years. All subjects completed the trial as planned and were included in the analyses of pharmacokinetic and safety variables.

Administration of 200 mg ritonavir twice daily for 3 days in the test treatment resulted in ritonavir plasma concentrations sufficient to effectively inhibit P-gp and CYP3A4.

Following administration of 20 mg BIBW 2992 alone, gMean $AUC_{0-\infty}$ and AUC_{0-tz} of BIBW 2992 were 165 ng·h/mL and 153 ng·h/mL, respectively; gMean maximum plasma concentrations were 7.71 ng/mL and were observed at a median t_{max} of 4.00 h after dosing, ranging from 0.50 to 5.00 h.

In combination with ritonavir, gMean $AUC_{0-\infty}$ of BIBW 2992 increased by 47.6% to 243 ng·h/mL, gMean AUC_{0-tz} increased by 49.0% to 228 ng·h/mL, and gMean C_{max} increased by 38.5% to 10.7 ng/mL. Median t_{max} was unchanged (4.00 h, ranging from 3.98 to 5.00 h). When comparing the plasma concentration-time profiles of BIBW 2992 with and without ritonavir, the distribution and elimination phases of BIBW 2992 appeared to be unaffected by ritonavir cotreatment. Also, the terminal half-life ($t_{1/2}$) of BIBW 2992 was unchanged (35.9 vs. 34.1 h for BIBW 2992 alone and in combination with ritonavir, respectively).

Adjusted gMean test/reference ratios for $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} and their 90% confidence intervals as well as intra-individual geometric coefficient of variation (gCV) values are summarised in the table below.

Parameter (N=22)	Adjusted gMean ratio (test/reference[1]) [%]	Two-sided 90% confidence interval		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$	147.6	133.7	162.9	19.2
AUC_{0-tz}	149.0	134.5	165.1	19.9
C_{max}	138.5	120.6	158.9	27.0

[1]Test = BIBW 2992 and ritonavir, reference = BIBW 2992 alone

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Safety results:

Each subject was administered a total dose of 40 mg BIBW 2992 and a total dose of 1200 mg ritonavir as planned.

Ten subjects (45.5%) reported AEs during the trial. Six subjects (27.3%) experienced AEs during the treatment with BIBW 2992 alone. Seven subjects (31.8%) reported AEs during the treatment with BIBW 2992 and ritonavir. The most frequently reported AE overall was diarrhoea (4 subjects), followed by headache (3 subjects), rhinitis (2 subjects), dry mouth, nasopharyngitis, and migraine (1 subject each). During the treatment with BIBW 2992 and ritonavir, 5 subjects experienced AEs that were assessed as drug-related by the investigator (diarrhoea in 4 subjects and dry mouth in 1 subject). No drug-related AEs were reported during the treatment with BIBW 2992 alone. All AEs were of either mild or moderate intensity and all AEs resolved without treatment. No deaths, no other serious AEs, and no AEs that led to discontinuation occurred during the trial.

There were no clinically relevant findings with respect to vital signs, ECG recordings, and laboratory parameters. Global tolerability was assessed as good for all 22 subjects in both treatment periods.

Conclusions:

When BIBW 2992 20 mg was given in combination with ritonavir 200 mg twice daily, $AUC_{0-\infty}$ of BIBW 2992 increased by 47.6% (90% CI 133.7%, 162.9%), AUC_{0-tz} increased by 49.0% (90% CI 134.5%, 165.1%), and C_{max} increased by 38.5% (90% CI 120.6%, 158.9%) compared with BIBW 2992 given alone. Median t_{max} of BIBW 2992 was 4.00 h with and without ritonavir. The distribution and elimination phases of BIBW 2992 appeared to be unaffected by ritonavir cotreatment. Also, the terminal half-life of BIBW 2992 was unchanged. Since previous studies revealed that CYP3A4 enzyme-catalysed metabolic reactions play a subordinate role for the metabolism of BIBW 2992 *in vivo* and CYP3A4-dependent N-demethylation was too low to be quantitatively detected in healthy volunteers, the increase in BIBW 2992 exposure in the presence of ritonavir can most likely be attributed to the inhibition of P-gp-mediated transport processes during the absorption phase of BIBW 2992.

Single doses of 20 mg BIBW 2992 given alone and in combination with ritonavir were safe and well tolerated by healthy subjects. There was no apparent correlation between AEs and the increase in BIBW 2992 exposure in the presence of ritonavir.