

## **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*.

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Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim			
Name of finished product:		EudraCT No.:				
Not applicable		2009-011909-16				
Name of active ingree	lient:	Page:				
BIBW 2992 / ritonavir		1 of 4	Synopsis No.:			
Module:		Volume:				
Report date:	Trial No. / U No.:	Dates of trial:	Date of revision:			
02 JUN 2010	1200.79 / U10- 1163-01	17 SEP 2009 – 14 DEC 2009	Not applicable			
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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 da compared to the bioavailability of a single oral dose of BIBW 2992 (20 m alone in healthy male volunteers (an open-label, randomised, two-way cro clinical phase I study)			BIBW 2992 (20 mg) after onavir (200 mg bid for 3 days) dose of BIBW 2992 (20 mg) , randomised, two-way crossover,			
Principal Investigator:						
Trial site: Boehringer Ing Biberach, Gerr		gelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, many				
<b>Publication (reference):</b> Data of this s		udy 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.			tonavir, an inhibitor of 4 (CYP3A4), on the			
Methodology:	This was an op administration Each subject u	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	entered: 22				
actual:	entered: 22	entered: 22				
	BIBW 2992 at treated: 22 at	BIBW 2992 and ritonavir: treated: 22 analysed (for primary endpoints): 22				
	BIBW 2992 a treated: 22 au	<ul><li>2 alone:</li><li>2 analysed (for primary endpoints): 22</li></ul>				
Diagnosis and main criteria for inclusion:Healthy male volunteers, age $\geq 21$ and $\leq 55$ years, body mass index $\geq 18$ . $\leq 29.9 \text{ kg/m}^2$			s, body mass index $\geq 18.5$ and			

Name of company: Boehringer IngelheimTabulated Trial ReportBoehring IngelheidName of finished product: Not applicableEudraCT No.: 2009-011909-16Image: Company: Description:Image: Company: Description:Name of active ingredient: BIBW 2992 / ritonavirPage: 2 of 4Synopsis No.:Module:Volume:Volume:Module:Trial No. / U No.: 1200.79 / U10- 1163-01Dates of trial: 17 SEP 2009 – 14 DEC 2009Date of revision: Not applicable	ger m served.					
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Investigational product 1: BIBW 2992 20 mg tablet						
dose: 20 mg (single dose)	20 mg (single dose)					
mode of admin.: Oral	Oral					
<b>batch no.:</b> B071003953	B071003953					
<b>Investigational product 2:</b> Ritonavir 100 mg capsule (Norvir <sup>®</sup> )	Ritonavir 100 mg capsule (Norvir <sup>®</sup> )					
dose: 200 mg twice daily	200 mg twice daily					
mode of admin.: Oral	Oral					
batch no.:72660VA (Abbott Laboratories Ltd.)	72660VA (Abbott Laboratories Ltd.)					
<b>Duration of treatment:</b> Test treatment: 3 consecutive days of treatment with 200 mg ritonavir tw daily combined with a single oral dose of 20 mg BIBW 2992 in the more the second day. Reference treatment: single oral dose of 20 mg BIBW 29 alone. The 2 BIBW 2992 administrations were separated by a wash-out p at least 21 days.	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:						
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Safety:Physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, analysis of adverse ev (AEs), and global tolerability assessment	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 analy variance (ANOVA) model including effects for 'treatment', 'period', 'sequ and 'subjects nested within sequence'. For the primary endpoints, 90% confidence intervals (CI) were computed, then back-transformed to the o scale to give the geometric mean (gMean) and interval estimates for the test/reference ratio.For all other parameters, descriptive statistics are presented.	$C_{0-tz}$ , and $C_{max}$ were log-transformed prior to fitting an analysis of VOVA) model including effects for 'treatment', 'period', 'sequence', nested within sequence'. For the primary endpoints, 90% atervals (CI) were computed, then back-transformed to the original the geometric mean (gMean) and interval estimates for the median e ratio.					

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SUMMARY – CONC	CLUSIONS:							
Clinical pharmaco results:	logy Twenty-two h mean age of th planned and v variables.	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.						
	Administratio resulted in rito and CYP3A4.	on of 200 mg ritonavir twice daily for 3 days in the test treatment onavir plasma concentrations sufficient to effectively inhibit P-gp.						
	Following adı AUC <sub>0-tz</sub> of BI gMean maxin a median t <sub>max</sub>	ministration of 20 mg BIBW 2992 alone, gMean AUC <sub>0-<math>\infty</math></sub> and BW 2992 were 165 ng·h/mL and 153 ng·h/mL, respectively; num plasma concentrations were 7.71 ng/mL and were observed at of 4.00 h after dosing, ranging from 0.50 to 5.00 h.						
	In combination with ritonavir, gMean AUC <sub>0-∞</sub> of BIBW 2992 increased by 47.6% to 243 ng·h/mL, gMean AUC <sub>0-tz</sub> increased by 49.0% to 228 ng·h/mL, ar gMean C <sub>max</sub> increased by 38.5% to 10.7 ng/mL. Median t <sub>max</sub> 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 britonavir 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 <sup>1</sup> ) [%]	Two-sided 90% confidence interval		Intra-individual gCV			
			Lower limit [%]	Upper limit [%]	[%]			
	AUC <sub>0-∞</sub>	147.6	133.7	162.9	19.2			
	AUC <sub>0-tz</sub>	149.0	134.5	165.1	19.9			
	C <sub>max</sub>	138.5	120.6	158.9	27.0			
	$^{1}\text{Test} = \text{BIBW}$	.992 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.						
	experienced A (31.8%) repor most frequent headache (3 su migraine (1 su 5 subjects exp (diarrhoea in 4 reported durin mild or moder other serious 4 trial. There were no recordings, an	ced AEs during the treatment with BIBW 2992 alone. Seven subjects reported AEs during the treatment with BIBW 2992 and ritonavir. The quently reported AE overall was diarrhoea (4 subjects), followed by e (3 subjects), rhinitis (2 subjects), dry mouth, nasopharyngitis, and v (1 subject each). During the treatment with BIBW 2992 and ritonavir, ts experienced AEs that were assessed as drug-related by the investigate ea in 4 subjects and dry mouth in 1 subject). No drug-related AEs were during the treatment with BIBW 2992 alone. All AEs were of either moderate intensity and all AEs resolved without treatment. No deaths, rious AEs, and no AEs that led to discontinuation occurred during the ere no clinically relevant findings with respect to vital signs, ECG					
<b>Conclusions:</b>	for all 22 subj When BIBW 2 daily, AUC <sub>0-xz</sub> AUC <sub>0-tz</sub> increa 38.5% (90% C Median t <sub>max</sub> of distribution ar ritonavir cotre Since previous reactions play CYP3A4-dep in healthy volu- ritonavir can r transport proc Single doses of ritonavir were correlation bei presence of rit	all 22 subjects in both treatment periods. hen BIBW 2992 20 mg was given in combination with ritonavir 200 mg twice ily, AUC <sub>0-<math>\infty</math></sub> of BIBW 2992 increased by 47.6% (90% CI 133.7%, 162.9%), JC <sub>0-tz</sub> increased by 49.0% (90% CI 134.5%, 165.1%), and C <sub>max</sub> increased by .5% (90% CI 120.6%, 158.9%) compared with BIBW 2992 given alone. edian t <sub>max</sub> of BIBW 2992 was 4.00 h with and without ritonavir. The stribution and elimination phases of BIBW 2992 appeared to be unaffected by onavir cotreatment. Also, the terminal half-life of BIBW 2992 was unchanged. nce previous studies revealed that CYP3A4 enzyme-catalysed metabolic actions play a subordinate role for the metabolism of BIBW 2992 <i>in vivo</i> and <i>X</i> P3A4-dependent N-demethylation was too low to be quantitatively detected healthy volunteers, the increase in BIBW 2992 exposure in the presence of onavir can most likely be attributed to the inhibition of P-gp-mediated nsport processes during the absorption phase of BIBW 2992. ngle doses of 20 mg BIBW 2992 given alone and in combination with onavir were safe and well tolerated by healthy subjects. There was no apparent rrelation between AEs and the increase in BIBW 2992 exposure in the esence of ritonavir.					