Clinical Study Synopsis for Public Disclosure

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2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Not applicable				
Name of active ingredient: BIIL 284 BS		**Page:**	**Number:**	
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Report date: 09 August 2002	**Number:** 543.31	**Study period (years):** Oct – Nov 2001		

Title of study:	Randomised, open-label, two-way crossover study in male healthy volunteers to investigate the relative bioavailability of BIIL 284 BS 5 mg Tablet FF in comparison to Tablet C after ingestion of a standardised meal.
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, Germany
Publication (reference):	Not applicable
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of 5 mg Tablet FF vs 5 mg Tablet C, safety and tolerability
Methodology:	Two-way crossover comparison of two treatments, randomised, open-label
No. of subjects entered:	
total:	16
each treatment:	16 – BIIL 284 BS 5 mg Tablet FF 16 – BIIL 284 BS 5 mg Tablet C
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 – 50 years, Broca-Index: ± 20%
Test product:	BIIL 284 BS Tablets
dose:	5 mg Tablet FF
mode of admin.:	Oral after standard breakfast
batch no.:	B 010 728
Duration of treatment:	One day at each treatment
Reference therapy:	BIIL 284 BS Tablets
dose:	5 mg Tablet C
mode of admin.:	Oral after standard breakfast
batch no.:	B 001 110

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Criteria for evaluation:

Efficacy: **Pharmacokinetics:**

C_{max}, AUC_{0-6}, AUC_{0-tz}, $AUC_{0-\infty}$ for BIIL 315 ZW (primary endpoints) as well as t_{max}, λ_z, t_{lag}, $t_{1/2}$, MRT_{tot}, CL/F and V_z/F for BIIL 315 ZW, individual plasma concentration versus time profiles for BIIL 315 ZW.

Safety: Blood pressure, pulse rate, ECG, adverse events, laboratory tests

Statistical methods: Criteria for bioequivalence: the two-sided 90% CIs for expected median intrasubject (intra-individual) ratios are contained in the range of 80-125% for $AUC_{0-\infty}$ and 80-125% for C_{max}. The statistical model was ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs were based on the residual error from ANOVA. Additionally, the corresponding point estimates for $AUC_{0-\infty}$ and C_{max} were provided. Descriptive analysis for all other parameters.

SUMMARY – CONCLUSIONS:

The objective of this randomised, open-label, single-dose, two-way crossover study was to investigate the relative bioavailability of BIIL 284 BS Tablet FF in comparison to the Tablet C at a dose of 5 mg after a standard breakfast in healthy male volunteers.

Pharmacokinetic results:

Plasma samples were analysed by HPLC-MS/MS (limit of quantification: 0.1 ng/mL).

Geometric means of the C_{max} , AUC_{0-6}, AUC_{0-tz}, and $AUC_{0-\infty}$ values for BIIL 315 ZW after a single oral dose of 5 mg BIIL 284 BS as Tablet FF and Tablet C in the fed state were as follows.

			Tablet FF		Tablet C	
Parameter	**Unit**	**N**	**gmean**	**gCV (%)**	**gmean**	**gCV (%)**
C_{max}	[ng/mL]	16	4.35	100	6.54	54.9
AUC_{0-6}	[ng·h/mL]	16	13.9	97.3	20.4	63.0
AUC_{0-tz}	[ng·h/mL]	16	20.8	116	27.8	72.4
$AUC_{0-\infty}$	[ng·h/mL]	16	24.0	111	31.0	71.2

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The geometric mean values for C_{max} , AUC_{0-6}, AUC_{0-tz}, and $AUC_{0-\infty}$ after oral administration of 5 mg BIIL 284 BS as Tablet FF were lower than the respective values obtained after oral administration of 5 mg BIIL 284 BS as Tablet C. Interindividual variability in the pharmacokinetic parameters was higher after administration of Tablet FF than after administration of Tablet C.

The 5 mg Tablet FF was inferior to Tablet C regarding peak exposure and extent of exposure. The point estimators for the C_{max} and AUC ratios (Tablet FF/Tablet C) suggest a mean reduction in C_{max} of 33.6% and a mean reduction in AUC_{0-6}, AUC_{0-tz}, $AUC_{0-\infty}$ of 31.9%, 25.2% and 22.7%, respectively, after administration of Tablet FF compared to Tablet C.

Ratio (Test/Reference)	**Parameter**	**Unit**	**N**	**Adjusted mean (%)**	**Two sided 90% C.I. (%)**	
					Lower limit	**Upper limit**
Tablet FF/ Tablet C	C_{max}	[ng/mL]	16	66.4	46.7	94.4
	AUC_{0-6}	[ng·h/mL]	16	68.1	49.7	93.3
	AUC_{0-tz}	[ng·h/mL]	16	74.8	52.6	106.3
	$AUC_{0-\infty}$	[ng·h/mL]	16	77.3	54.9	108.7

Bioequivalence was not shown for any of the parameters. All point estimators were lower than 80%. The confidence intervals were relatively wide due to the high intraindividual variability of BIIL 315 ZW pharmacokinetics and the relative small sample size. For C_{max} and AUC_{0-6} a significant difference between the 5 mg Tablet FF and 5 mg Tablet C was shown on the 10% significance level.

In addition the median t_{lag} and median t_{max} values for Tablet FF (0.5 h, 3 h) and Tablet C (0.00 h, 2.00 h) indicate that BIIL 315 ZW was more rapidly available in the systemic circulation after administration of Tablet C than after administration of Tablet FF.

			Tablet FF		**Tablet C**	
Parameter	**Unit**	**N**	**gmean**	**gCV (%)**	**gmean**	**gCV (%)**
$t_{lag\#}$	[h]	16	0.50	0.00-1.00	0.00	0.00-1.00
$t_{max\#}$	[h]	16	3.00	1.00-5.00	2.00	1.00-4.00
$t_{1/2}$	[h]	16	8.56	77.3	8.13	95.5
MRT_{tot}	[h]	16	9.39	42.8	8.03	45.2
CL/F	[mL/min]	16	4150	111	3210	71.2
V_z/F	[L]	16	3080	89.0	2260	97.5

median and range is given

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The pharmacokinetic parameters of one individual (subject [redacted] determined after administration of Tablet FF were much lower in comparison to the other 15 subjects who received Tablet FF. The C_{max} and $AUC_{0-\infty}$ values were 14.2 and 15.3-fold lower than the respective geometric mean values based on all 16 subjects. For Tablet C the lowest individual and the geometric mean values for C_{max} and $AUC_{0-\infty}$ differed by factors of 2.99 and 4.30, respectively. Administration of Tablet C to subject [redacted] resulted in midrange values for C_{max} and $AUC_{0-\infty}$ indicating that in principle absorption of BIIL 284 BS / BIIL 315 ZW is possible for subject No. 9.

A cross-study comparison revealed that the geometric mean C_{max} and $AUC_{0-\infty}$ values for the 5 mg Tablet FF and 5 mg Tablet C were about 2 to 2.5-fold higher than predicted from the 75 mg Tablet C data.

Safety results:

Due to the observations made in this study described in this report BIIL 284 BS was safe and well tolerated in healthy male volunteers following administration of single doses of 5 mg BIIL 284 BS as tablet C and as tablet FF in fed condition. No adverse events were reported in this trial. The safety parameters blood pressure, pulse rate, ECG and standard laboratory tests did not reveal any obvious clinically significant drug-related changes. With the conditions investigated in this trial BIIL 284 BS was free of any side effects which would raise objections to further clinical studies in volunteers or patients.

Conclusions:

- Peak exposure and total extent of exposure (C_{max} and $AUC_{0-\infty}$) after administration of 5 mg Tablet FF were reduced by about 34% and 23% compared to 5 mg Tablet C. However, the relevance of this finding with regard to efficacy is unclear as no exposure-response relationship has been determined yet.

- The observation of one extreme low plasma concentration profile of BIIL 315 ZW after administration of 5 mg Tablet FF should be further investigated in future studies.