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***.

3. SYNOPSIS AND TRIAL ABSTRACT

3.1 SYNOPSIS

Name of company: Boehringer Ingelheim Pharma KG		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product:				
Name of active ingredient: BIBB 515 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: **November 5, 1998**	**Number:**	**Study period (years):** **June/July 1998**		

Title of study:	Single-dose pharmacokinetics of 2.5 mg BIBB 515 BS and effect of food after oral administration of capsules to healthy subjects (randomized, 2-way-cross-over, open study).
Investigator:	[redacted]
Study centre(s):	Human Pharmacology Center Boehringer Ingelheim Pharma KG, D-88397 Biberach an der Riss
Publication (reference):	not yet published
Clinical phase:	I
Objectives:	To assess the effect of a breakfast (40 g fat) on single dose pharmacokinetics of a 2.5 mg BIBB 515 dose in capsules as well as the tolerability of BIBB 515 BS capsules. Monoepoxysualene in plasma (MES) for development of HPLC-MS method
Methodology:	Open randomized two-way cross-over comparison
No. of subjects entered:	
total:	8 healthy male subjects
each treatment:	8 healthy male subjects
Diagnosis and main criteria for inclusion:	Healthy male subjects
Test product:	BIBB 515 BS 1.25 mg capsules immediately after breakfast (40 g fat)
dose:	2.5 mg BIBB 515 BS (2 capsules)
mode of admin.:	p.o.
batch no.:	Drug formulation: 1.25 mg capsule BIBB 515 BS KAH 99 1A1A, lot B980313
Duration of treatment:	single administration
Reference therapy:	BIBB 515 BS 1.25 mg capsules fasted
dose:	2.5 mg BIBB 515 BS (2 capsules)
mode of admin.:	p.o.
batch no.:	Drug formulation: 1.25 mg capsule BIBB 515 BS KAH 99 1A1A, lot B980313

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Criteria for evaluation:	
Efficacy:	Pharmacokinetics: Non-compartmental analysis: C_{max}, $AUC_{0-\infty}$, AUC_{0-t}, t_{max}, λ_z, $t_{½}$, MRT_{tot}, CL/f, V_z/f
Safety:	Pulse rate, systolic and diastolic blood pressure, laboratory, adverse events
Statistical methods:	90 % confidence intervals for pharmacokinetic parameters, descriptive statistics

SUMMARY - CONCLUSIONS:

Efficacy results:

Pharmacokinetics:

BIBB 515 plasma and urine concentrations were analyzed by validated HPLC assays with fluorescence detection. Assay precision and accuracy was within 12.0 % and ±6.8 % for plasma and within 13.0 % and ±4.1 % for urine. Limits of quantification were 0.5 ng/mL for plasma and 10 ng/mL for urine.

The male healthy subjects had a mean (range) age of 32.6 (21-45) years, a mean (range) weight of 82.1 (60-100) kg and a mean height of 180 (163-191) cm).

BIBB 515 was not detected in any urine sample. Thus urinary excretion was at least less than 1 % taking the dose of 2.5 mg and a urine volume of 2 L into account.

A more hydrophilic metabolite with a similar concentration-time profile and regularly higher concentrations than BIBB 515 was noted in plasma. The metabolite is not identical to one of the known degradation products BIBB 671 or BIBB 672.

The drug was absorbed from the capsule in fasted state with geometric mean (%gCV) C_{max} values of 5.78 ng/mL (37.0%) one hour after dose, while absorption was slightly delayed after a concomitant breakfast with C_{max} values of 4.67 ng/mL (32.6 %) occurring 2.5 hour after dosing. AUC values increased moderately by 37 % from fasted 12.9 ng·h/mL (62 %) to the fed state 17.7 ng·h/mL (76 %). In summary, a moderate mean food effect was noted for the capsule, but the high variability of this food effect (test/reference ratios ranging from 0.5 to 3.0) and the high interindividual variability of the drug limits the validity of this statement.

A comparison to an earlier trial performed with BIBB 515 suspension (2.5 mg dose) in fasted state revealed similar C_{max} values (5.78 ng/mL vs 4.8 ng/mL for suspension) and moderately higher AUC0-t values (11.0 ng·h/mL vs 10.7 ng·h/mL for suspension). This means that the capsules have at least a similar bioavailability in comparison to the suspension.

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Results of the non-compartmental pharmacokinetic evaluation (n=8).

		2.5 mg BIBB 515 after breakfast				2.5 mg BIBB 515 BS fasted					
		gmean	%gCV	a.mean	%CV	gmean	%gCV	a.mean	%CV	Ratio	90 % CI
C_{max}	[ng/mL]	4.67	32.6	4.88	33.0	5.78	37.0	6.13	40.4	0.808	0.633-1.03
t_{max}	[h]	# 2.5	§ 1-3	2.3	34.6	# 1.0	§ 0.5-2	1.1	39.4	--	--
AUC_{0-t}	[ng/mL]	15.7	78.7	19.2	67.7	11.0	60.0	12.8	64.3	--	--
$AUC_{0-\infty}$	[ng·h/mL]	17.7	76.0	21.3	65.5	12.9	62.0	15.0	64.0	1.37	1.05-1.80
$t_{½}$	[h]	&2.0	61.1	&2.3	56.3	&1.6	101	&2.2	81.0	1.24	0.718-2.14
MRT_{tot} &	[h]	4.04	44.1	4.33	36.6	2.90	49.5	3.20	47.8	1.39	1.04-1.85
CL/f &	[L/min]	2.36	76.1	2.90	77.1	3.23	62.0	3.66	47.6	0.729	0.556-0.955
Vz/f &	[L]	407	33.5	428	36.8	450	43.8	492	52.9	0.903	0.603-1.35

#: median, §: range, &: terminal phase regularly not detected, gmean: geometric mean, a.mean: arithmetic mean, ratio (=point estimate) ratio of individual geometric means test (after breakfast) /reference (fasted)

MES results will be reported separately in amendment as foreseen in the trial protocol.
Safety results:
Influenza like symptoms in one subject (in the wash-out phase) and headache in another were the only adverse events reported.

Conclusions:
Concomitant food was associated with a delayed absorption (t_{max} 2.5 h vs 1 h) and a moderately higher (+37 %) bioavailability for BIBB 515 BS. Capsules had an at least similar bioavailability like BIBB 515 suspension. The urinary excretion of the drug is at least less than 1 % of the dose. BIBB 515 BS was well tolerated.