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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: n. a.				
Name of active ingredient: BIBB 1464 MS		**Page:**	**Number:**	
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Report date: 18 February 2000	**Number:** 1178.1	**Study period (years):** 1999		

Title of study:	Safety/Tolerability, Pharmacokinetics, And Pharmacodynamics Of Single Oral Doses of 0.25 mg, 0.75 mg, 2 mg, 6 mg, and 10 mg BIBB 1464 MS (Tablet) in Healthy Male Subjects, Combined With Preliminary Evaluation of Relative Bioavailability and Effect of Food of the Dose of 0.75 mg Or 2 mg Or 6 mg (Two-Stage Trial Design With Randomised Double Blind Placebo Controlled Rising Dose Phase and Subsequent Randomised, Open Parallel Group Phase).
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Biberach, Germany
Publication (reference):	n.a.
Clinical phase:	I
Objectives:	The objectives were to evaluate in healthy male volunteers: • the safety/tolerability of single doses of BIBB 1464 MS; • the pharmacokinetics of single doses of BIBB 1464 MS; • the pharmacodynamic response to single doses of BIBB 1464 MS in terms of monoepoxysqualene (MES) plasma concentrations; • the relative bioavailability of the BIBB 1464 MS tablet formulation versus solution (in a preliminary sense), • possible effects of concomitant food intake on the single dose pharmacokinetics of the BIBB 1464 MS tablet formulation (in a preliminary sense). The investigation of the pharmacokinetic and pharmacodynamic dose-response-profile aimed at selecting the doses to be carried forward from this trial to the subsequent 2 week tolerability- and proof-of-concept study.
Methodology:	Rising dose phase: placebo controlled, double blind, randomized per dose level; Bioavailability phase: randomised parallel groups, open treatments.
No. of subjects entered: **total:**	Rising dose phase: 60 subjects entered, 58 subjects treated; Bioavailability phase: 24 subjects entered, 23 subjects treated, Overall: A total of 73 subjects were entered (11 of them in both phases) and a total of 70 subjects were treated (11 of them in both trial phases); since subjects from the first, second, and fourth cohort of the rising dose phase could be re-randomised in the bioavailability phase.

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each treatment:	Rising dose phase: 0.25mg group: 10 subjects entered, 10 treated 0.75mg group: 10 subjects entered, 10 treated 2 mg group: 10 subjects entered, 10 treated 6 mg group: 10 subjects entered, 10 treated 10 mg group: 10 subjects entered, 9 treated Placebo: 10 subjects entered, 9 treated Bioavailability phase: 2 mg tablet: 12 subjects entered, 11 treated 2 mg solution: 12 subjects entered, 12 treated
Diagnosis and main criteria for inclusion:	healthy male subjects
Test product:	BIBB 1464 MS tablets (0.25 mg, 2 mg)
dose:	0.25, 0.75, 2, 6, 10 mg
mode of admin.:	p.o. after dinner at 7 PM with 200 ml tap water
batch no.:	0.25 mg tablet: Code BIBB 1464 MS TA 99 1A 1B, batch B990603 '0.25 mg' placebo: Code BIBB 1464 MS TA 99 1A 0A, batch B990608 2 mg tablet: Code BIBB 1464 MS TA 99 2A 1B, batch B990605 '2 mg' placebo: Code BIBB 1464 MS TA 99 2A 0A, batch B990611
Duration of treatment:	single administration except for second bioavailability period
Reference therapy:	Bioavailability Phase: BIBB 1464 MS tablets and solution in fasted state
dose:	2 mg
mode of admin.:	p.o. fasted at 7 PM with 200 ml tap water (solution: additional 140 mL)
batch no.:	2 mg tablet: Code BIBB 1464 MS TA 99 2A 1B, batch B990605 2 mg solution: Code BIBB 1464 MS LO 99 1A 1A, batch B990602
Criteria for evaluation:	
Pharmacodynamics:	monoepoxysqualene (MES) plasma concentrations and derived parameters
Pharmacokinetics:	drug plasma concentrations and derived parameters
Safety:	adverse events, safety laboratory parameters, vital signs (systolic/diastolic blood pressure, pulse rate), physical examination,12-lead ECG, global tolerability assessment by the investigator

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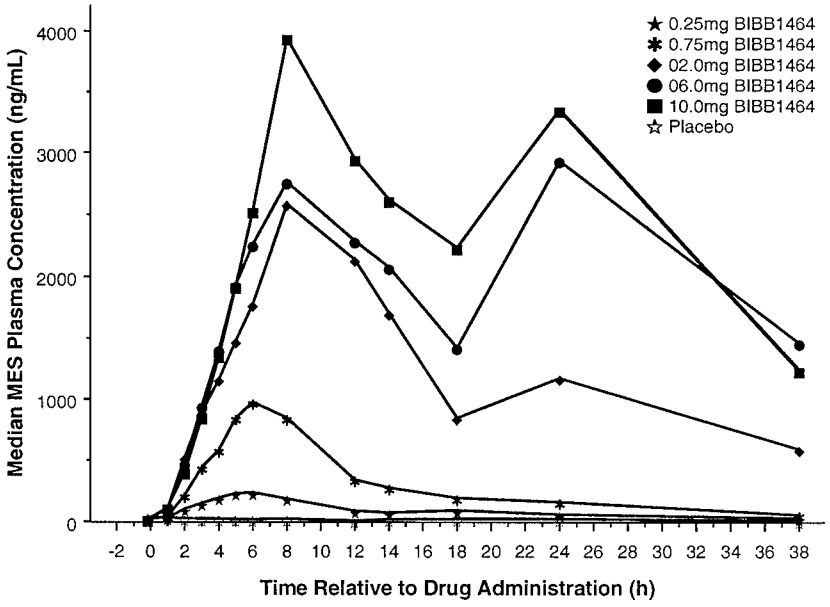
Statistical methods: descriptive statistical methods, analysis of variance for log-transformed pharmacokinetic parameters (standard two-sample model, power model, dose-division model), nonlinear regression for pharamcodynamic dose-response relationship

SUMMARY - CONCLUSIONS:

Pharmacodynamic results:

Elevation of MES plasma concentrations is considered as a marker for inhibition of cholesterol biosynthesis in the liver.

MES plasma concentrations at all doses were clearly elevated over 24 hours compared to placebo. The increase in MES plasma concentrations and derived parameters was dose-dependent. A distinct second peak at roughly 24 hours after drug administration was observed for the 2 mg dose group and higher dose groups.



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For the 10 mg dose of BIBB 1464 MS, MES plasma concentrations were also determined for later time-points (up to 146 hours after drug administration). The median MES plasma concentration was still 1687ng/mL after 146 hours.

MES parameters were also increased compared to placebo in all active treatment groups in a dose-dependent way. The increase in MES parameters was clearly less pronounced for the dose interval from 2 mg to 10 mg (as opposed to the dose interval from 0.25 mg to 2 mg), especially for the MES parameters computed over short time intervals following drug administration. However, it is not clear from the data whether a plateau for these parameters was reached even with the 10 mg dose.

Pharmacokinetic results:

BIBB 1464 was relatively slowly absorbed after intake in the evening with maximum drug plasma concentrations observed after median times of 4.5 hours to 14 hours. Multiple drug concentration peaks were regularly seen after a dose of 2 mg and above. Drug concentrations increased more than proportional to dose indicating any type of saturable first-pass effect and showed a remarkably low variability at higher doses. Drug concentrations were even 146 hours after ingestion of a 10 mg dose high above the limit of quantification (gMean 1.47 ng/mL, limit: 0.10 ng/mL). The observed elimination half-life of 56 hours (10 mg) could therefore even underestimate the terminal elimination half-life. This might be supported by unexpectedly high drug concentrations in all four subjects of the bioavailability phase who received 6 mg drug three weeks before. Even subjects with 0.75 mg pretreatment five weeks before showed higher drug concentrations than the remaining subjects. All pretreated subjects were therefore excluded in the table below. Urinary excretion of parent compound was negligible with a geometric mean of 0.578 % (42.5 % gCV) for a 10 mg dose in the first 38 hours after drug intake. Renal clearance was 3.3 mL/min and thus 1-2 % of the total clearance.
Group comparisons excluding these subjects showed that the relative bioavailability of BIBB 1464 tablets was 112 % of the value for solution. Concomitant food resulted in geometric mean $AUC_{0\text{-}38h}$ values by 26 % higher than given fasted.

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		Tablet fed					Tablet fasted	Solution fasted
Dose	[mg]	0.25	0.75	2	6	10	2	2
	n		10	10	10	9	6	9
C_{max}	gMean	nv	0.407	1.75	6.03	11.7	1.55	1.42
[ng/mL]	%gCV	nv	(26.3)	(17.1)	(17.0)	(24.8)	(35.4)	(18.4)
t_{max}	median	nv	4.5	5.5	14	8	5.5	5
[h]	range	nv	(3-5)	(3-14)	(6-14)	(2-18)	(4-14)	(4-14)
AUC_{0-38h}	gMean	nv	3.01#	42.2	157	294	33.4	30.2
[ng.h/mL]	%gCV	nv	(70.1)	(17.3)	(13.6)	(17.6)	(15.1)	(17.4)
$NAUC_{0-38h}$ #	gMean	nv	4.02	21.1	26.4	29.4	16.7	15.1
AUC_{0-oo}	gMean	nv	cnp	cnp	cnp	741	90.7	81.0
[ng.h/mL]	%gCV	nv				(10.5)	(14.6)	(13.9)
MRT_{tot}	gMean	nv	cnp	cnp	cnp	78.4	79.6	80.0
[h]	%gCV	nv				(16.8)	(18.7)	(10.9)
$t_{½}$	gMean	nv	cnp	cnp	cnp	56.1	54.2	55.0
[h]	%gCV	nv				(17.2)	(20.2)	(11.7)
CL/f	gMean	nv	cnp	cnp	cnp	225	368	411
[mL/min]	%gCV	nv				(10.5)	(14.5)	(13.9)

#: [ng.h/mL/mg]

#: AUC_{0-tf}, cnp: calculation not possible, nv: no drug concentration above the limit of quantification (0.10 ng/mL)

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Safety results:

Adverse events after intake of study medication were reported for a total of five subjects during the rising dose phase of the trial, and for only one subject during the bioavailability phase.

None of these adverse events was assessed as drug related by the investigator. With the exception of one serious AE (hematemesis due to Mallory-Weiss esophageal lesion induced by vomiting), the intensity of the AEs was classified as mild, and no therapy was required. All subjects recovered prior to the end-of-trial examination or follow-up was considered as sufficient at the end of study.

All adverse events in the rising dose phase occurred in the highest dose group (10 mg BIBB 1464 MS). The corresponding p-value is highly significant ($p<0.01\%$ in Fisher's exact test), indicating that this accumulation of adverse events did almost certainly not occur just by chance. In view of the nature of these adverse events this accumulation seems to be caused by a local epidemic gastrointestinal infection at the time this cohort was treated. Since due to discontinuation of a subject randomised to placebo, in this cohort of the rising dose phase virtually no control group was treated in parallel, an influence of study treatment can however not definitely be excluded.

At the end-of-trial examination, no new or worsened findings were reported from the general physical examination and the 12-lead ECG examination. Global tolerability was judged as good for all subjects by the investigators. Except for the unexplained mild increase of bilirubin (with no abnormalities in liver function tests detected) in the 10 mg dose group the analysis of vital sign parameters and safety laboratory parameters did not reveal treatment effects or changes of clinically relevant magnitude.

Conclusions:

Pharmacodynamics: Following the present explanation for the second peak phenomenon (negative regulatory feedback loop from squalene cyclase to HMG-CoA-reductase), the first MES peak in plasma represents the actual inhibition of cholesterol biosynthesis. An essentially complete inhibition of cholesterol biosynthesis should thus be achieved already with the 2 mg dose of BIBB 1464 MS. The flattening of the dose-response curves for MES parameters supports this hypothesis to some extent, although a plateau for the MES parameters was not reached at the 2 mg dose, and possibly not even with the 10 mg dose. Assuming nearly complete inhibition of cholesterol biosynthesis with the 2 mg dose, it is conjectured that multiple administration of BIBB 1464 MS leading to comparable or even lower drug exposure would result in pronounced and statistically significant lipid lowering effects.

Pharmacokinetics: BIBB 1464 showed a saturable first pass effect and an elimination half-life of 56 hours. The terminal elimination half-life is expected to be longer than 56 hours.

Safety: Overall, single doses of BIBB 1464 MS up to 6 mg were safe and well tolerated in this study. It is assumed that the accumulation of adverse events observed in the 10 mg treatment group was caused by a local epidemic gastrointestinal infection. Since virtually no control group was treated in parallel in this cohort, an influence of study treatment can however not definitely be excluded.