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		**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: January 19, 1999	**Number:** Trial No.: 525.3	**Study period (years):** July to September, 1998		

Title of study:	Pharmacodynamics, preliminary pharmacokinetics and tolerability after multiple oral doses of 2.5 mg o.d. BIBB 515 BS (capsule) or pravastatin 20 mg over 2 weeks in hyperlipemic healthy male subjects (parallel group comparison, randomized, placebo controlled, partly double blind [pravastatin open]).
Investigator:	[redacted]
Study centre(s):	Human Pharmacology Centre, Boehringer Ingelheim Pharma KG, Biberach / Riss
Publication (reference):	None
Clinical phase:	1
Objectives:	Investigation of pharmacodynamics (inhibition of oxidosqualene cyclase, MES as marker), effect on routine lipid profile parameters, safety and preliminary pharmacokinetics.
Methodology:	Randomised, partly double-blind (pravastatin open), placebo controlled, parallel group design.
No. of subjects entered:	
total:	enrolled 67, entered 60, completed 60
each treatment:	20
Diagnosis and main criteria for inclusion:	hyperlipemic ($\geq$ 5.4 mmol/L) healthy male subjects
Test product:	BIBB 515 BS 1.25 mg capsules
dose:	2.5 mg (two capsules)
mode of admin.:	p.o. with 200 mL water after dinner in the evening at 8 PM
batch no.:	BIBB 515 BS KAH 99 1A1A; lot B980313 (expiry date 30.09.1998)
Duration of treatment:	14 days

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Reference therapy:	placebo matching with BIBB 515 BS 1.25 mg capsules
dose:	-
mode of admin.:	p.o. with 200 mL water after dinner in the evening at 8 PM
batch no.:	BIBB 515 BS KAH 99 1A0A; lot B980309 (expiry date 30.09.1998)
Reference therapy:	pravastatin
dose:	20 mg
mode of admin.:	p.o. with 200 mL water after dinner in the evening at 8 PM
batch no.:	BIBB 515 BS TA 99 1A2A; B98309 (expiry date 30.09.1998)
Duration of treatment:	14 days

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Criteria for evaluation:

Efficacy: Mono-epoxy squalene (MES), lipid profile (Total-Cholesterol, LDL-, VLDL-, HDL-Cholesterol, apolipoprotein B, lipoprotein(a) [Lp(a)], triglycerides); preliminary BIBB 515 BS multiple dose pharmacokinetic parameters and metabolites in urine.

Safety: Adverse events, Laboratory, vital sign parameters (PR, BP, body weight), ECG, examination of eye lens and general physical examination.

Statistical methods: Descriptive statistics, (exploratory) analysis of variance / covariance, correlation analysis

SUMMARY - CONCLUSIONS:

Efficacy results:

Pharmacodynamic results: 1) Squalene cyclase inhibition. The surrogate marker for squalene cyclase inhibition, monoepoxysqualene plasma concentration, was clearly elevated in the BIBB 515 BS treatment group. Median MES $C_{max,sd}$ was 291.0 ng/mL for BIBB 515 BS compared to 31.5 ng/mL for placebo, median MES $C_{max,ss}$ was 1038.0 ng/mL for BIBB 515 BS compared to 43.0 ng/mL for placebo, and MES $C_{trough,ss}$ was 192.3 ng/mL for BIBB 515 BS compared to 30.0 for placebo ($p<0.1\%$ for each of the three parameters).

2) Effects on lipid profile at steady state. Mean percent reduction from baseline in Total-Cholesterol was 9.9% for BIBB 515 BS compared to 7.4% in the placebo group; for LDL-Cholesterol, the corresponding figures were 9.5% versus 4.8%. These differences were neither statistically significant nor clinically meaningful ($p=40.8\%$ and $p=29.0\%$, respectively). A posteriori power calculations showed that the trial had 90% power to detect a delta of 10%. The Pearson correlation coefficients for association between the two steady state MES parameters ($C_{max,ss}$ and $C_{trough,ss}$), pharmacokinetic parameters ($C_{max,ss}$ and AUC_{ss}), and percentage changes after two weeks in Total- and LDL-Cholesterol were generally significant and above 50% in modulus (the only exception being the correlation between $C_{max,ss}$ for drug and $C_{max,ss}$ for MES for which the correlation coefficient was 41.1% with $p=8.1\%$). Corresponding Pearson correlations with MES $C_{max,sd}$ were clearly weaker, but a

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nonparametric analysis showed that this was at least in part due to an extreme MES $C_{max,sd}$ value.The results of the analysis of apolipoprotein B data paralleled those obtained for Total- and LDL-Cholesterol to some extent. No treatment effects were evident on HDL-Cholesterol and triglycerides.
For lipoprotein (a), there was a mean percent increase after two weeks of 29.5% for the BIBB 515 BS treatment group (significantly larger than the placebo mean increase of 1.2%, p=0.6%). However, the reliability of the lipoprotein (a) data was questionable as many measurements yielded results below the limit of quantification.

3) Pharmacokinetic results: Geometric mean (%gCV) maximum drug concentrations after the first dose were lower (1.27 ng/mL, 67.6 %) than expected from a previous Phase I trial (trial 525.4: 4.67 ng/mL in fed state). This may be caused by the slower absorption (t_{max} 5 h vs 2.5 h in the previous trial) after administration in the evening. BIBB 515 concentrations rose about three times from the first to the last dose, suggesting again a saturable first pass effect in this dose range. Geometric mean (% gCV) $C_{max,ss}$ in steady state was 4.20 ng/mL (55 %) and was observed 4 hours post dose (range 1-12 h). AUC_{ss} was 36.9 ng. *h/mL (67.3 % gCV) which corresponds to an apparent oral clearance of 1.13 L/min. This exceeds the liver plasma flow and suggests substantial presystemic elimination. The calculated geometric mean elimination half-life of 9.1 h (84.8 % gCV) seems to underestimate the real value, which may in the range of 15 hours. This may indicate the diffusion back into circulation from a peripheral tissue compartment as many measurements yielded results below the limit of quantification.

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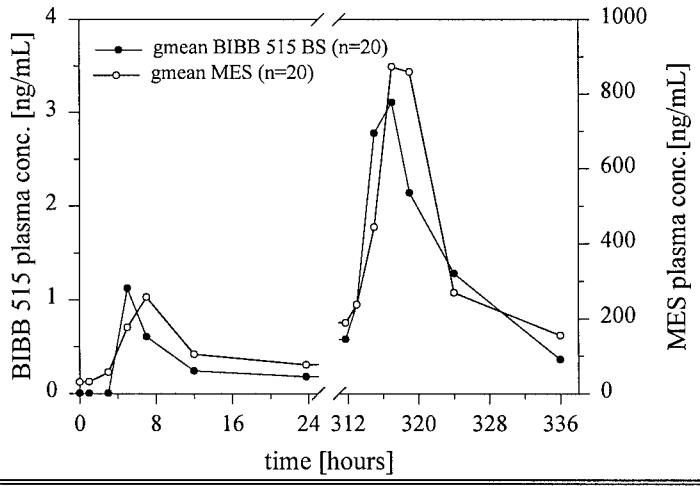
Results of the noncompartmental pharmacokinetic evaluation (N=20 except for C_{max} and t_{max}: N=19):

		gmean	%gCV	amean	% CV
C_{max}	[ng/mL]	1.27	67.6	1.51	61.7
t_{max}	[h]	# 5	§ 3-7	4.7	25.7
$C_{max,ss}$	[ng/mL]	4.20	55.0	4.68	43.0
$t_{max,ss}$	[h]	# 4	§ 1-12	4.55	52.6
λ_z	[h-1]	0.0760	84.8	0.0987	79.5
$t_{½}$	[h]	9.1	84.8	11.7	79.0
AUC_{ss}	[ng.h/mL]	36.9	67.3	43.0	50.9
MRT_{tot}	[h]	14.5	45.5	15.8	43.5
CL/f	[L/min]	1.13	67.3	1.38	77.0
V_z/f	[L]	892	68.8	1.11	84.3

#: median, §: range

geometric mean plot:



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Safety Results:

Only few adverse events were reported, all of them mild, transient, and not related to study treatment. The incidence rates of adverse events were comparable between the treatment groups. The only AEs which occurred in more than one subject in any of the treatment groups were headache and influenza-like symptoms.
No clinically relevant findings were reported from physical examination, 12-lead ecg, and eye lens examination at the end of trial.
There were no clinically relevant changes in vital sign- or laboratory parameters during the study.

Conclusions:

From the analysis of MES data, there is clear evidence for inhibition of squalene cyclase under treatment with 2.5mg BIBB 515 BS o.d. However, the degree of inhibition might have been weak, and relevant lipid lowering effects of treatment at this dose level can be excluded. On the other hand, percentage reductions in Total- and LDL-Cholesterol were correlated with drug exposure (measured by pharmacokinetic parameters) and degree of inhibition of squalene cyclase (measured by MES plasma concentration parameters). It is therefore conjectured that higher drug exposure would result in increased pharmacodynamic and clinical response.

2.5 mg BIBB 515 BS once daily over 14 days in the evening generated geometric mean maximum drug concentrations of 4.2 ng/mL (55.0 %gCV, range 1.1-9.4 ng/mL) in steady state occurring 4 hours post dose. The nonlinear pharmacokinetic behaviour due to a saturable first pass effect was confirmed. A three-fold increase in AUC_{ss} (to a range of 100-120 ng.h/mL instead of the observed value of 36.9 ng.h/mL) might possibly generated a percent cholesterol reduction comparable to that of 20 mg pravastatin.

Treatment with 2.5 mg BIBB 515 BS o.d. over two weeks was safe and well tolerated in healthy male subjects.