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***.

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: December 04, 2000	**Number:** 1178.2	**Study period (years):** 2000		

Title of study:	Pharmacodynamics, preliminary pharmacokinetics and tolerability after multiple oral doses of 0.25 mg, 0.5 mg and 1 mg o.d. BIBB 1464 (tablet) or pravastatin 20 mg over 2 weeks in hyperlipemic healthy male subjects (parallel group comparison, randomized, placebo controlled, partly double blind [pravastatin open]).
Investigators:	[redacted]
Study center(s):	[1]Human Pharmacology Centre Boehringer Ingelheim Pharma KG, 88397 Biberach an der Riss, Germany [2]Human Pharmacology Centre Boehringer Ingelheim Pharma KG, 55216 Ingelheim am Rhein, Germany
Publication (reference):	not applicable
Clinical phase:	I
Objectives:	Lipid lowering effect, investigation of pharmacodynamics (inhibition of oxidosqualene cyclase, MES as marker), safety/tolerability and preliminary pharmacokinetics.
Methodology:	A randomized, partly double-blind, double dummy (pravastatin open), placebo controlled, parallel group design study.
No. of subjects entered:	
total:	100 subjects in three subsequent phases:
each treatment:	• First pilot phase: 10 subjects (2 each treatment group) without loading dose; • second pilot phase: 10 subjects (2 for each treatment group) with loading dose (3x 0.25 mg viz. 3x 0.5 mg viz. 3x 1 mg on day 1); • main trial phase: 80 subjects (18 for each treatment group) with or without loading dose depending on preliminary results or the pilot phases.
Diagnosis and main criteria for inclusion:	hyperlipemic healthy male subjects
Test product:	BIBB 1464 MS BIBB 1464 MS
dose:	0.25 mg tablet 2 mg tablet dose groups: 0.25mg, 0.5mg, 1mg (second pilotphase 3x0.25mg, 3x0.5mg, 3x 1mg on day one)
mode of admin.:	p.o.
batch no.:	B990603 B990605

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Reference therapy:	Placebo	Placebo	Pravastatin
dose:	0.25 mg tablet	2 mg tablet	20 mg
	dose groups: placebo according to BIBB 1464 MS, pravastatin 1x20mg		
mode of admin.:	p.o.		
batch no.:	B990608	B990611	112A
Duration of treatment:	14 days for all treatments		
Criteria for evaluation:			
Efficacy:	Lipid profile (total cholesterol, LDL-, VLDL-, HDL-cholesterol, apolipoprotein B, lipoprotein(a) [Lp(a)], triglycerides); monoepoxysqualene plasma concentrations; large HDL, large VLDL, LDL particle size concentration, average LDL particle size; preliminary BIBB 1464 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, eye lens opacity measurements, global tolerability assessment by the investigator.		
Statistical methods:	Analysis of variance (ANOVA), descriptive statistical methods.		

SUMMARY - CONCLUSIONS:

Efficacy results:

The primary per protocol analysis population (PP1) included 88 of 100 treated subjects. This population was considered in the primary analysis of total cholesterol and LDL cholesterol, in the secondary analysis of other traditional lipid parameters (HDL cholesterol, triglycerides/VLDL cholesterol, apolipoprotein B, and lipoprotein (a)), and in the evaluation of monoexpoxysqualene (MES) plasma concentrations. For the secondary lipid profile parameters that were determined using the NMR technique (large HDL, large VLDL, LDL particle concetration, and average LDL particle size), the per protocol analysis population (PP2) included 64 subjects. In addition for all lipid profile endpoints, a limited evaluation was also done for an intention-to-treat population (ITT) which included all 100 treated subjects. The analysis population for steady state pharmacokinetics consisted of the 56 BIBB 1464 MS treated subjects who had received the planned number of 14 doses.

The treatment groups were assessed as comparable regarding standard demographic data and baseline lipid data.

The primary study endpoints were percentage change from baseline after two weeks in total cholesterol and LDL cholesterol.

For total cholesterol, mean percent reductions after two weeks were 14.84% for the lowest BIBB dose group (0.25mg), 12.25% for the medium BIBB dose (0.50mg), and 16.45% for the highest BIBB dose group (1mg) under study.

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In comparison, mean percent reductions were 7.26% for the placebo control group, and 20.69% for the 20mg pravastatin reference group.

For LDL cholesterol, mean percent reductions after two weeks were 17.33% for the lowest BIBB dose group (0.25mg), 14.17% for the medium BIBB dose group (0.50mg), and 19.97% for the highest BIBB dose group (1.0mg) under study. In comparison, there was a 9.13% reduction under placebo, and a 27.18% reduction in the pravastatin reference group.

Group comparisons versus placebo were significant for the highest BIBB dose group (1mg, p=0.0091 for total cholesterol and p=0.0085 for LDL cholesterol), but not for the medium dose group (0.50mg, p=0.1232 for total cholesterol and p=0.1861 for LDL cholesterol). The primary conclusion therefore is that BIBB 1464 MS treatment at 1mg o.d. over two weeks lowers total cholesterol and LDL cholesterol in hyperlipemic, otherwise healthy male subjects.

This result of the primary analysis is considered as a clinical proof of concept for the novel lipid lowering mechanism of action of BIBB 1464 MS (inhibition of oxidosqualene cyclase).

As expected, the results for apolipoprotein B and LDL particle concentration were very similar to the corresponding results observed for total cholesterol. This confirmed the robustness of the primary conclusion, which was also established by the results that were obtained using different statistical methods.

For HDL cholesterol, mean percent reductions from baseline were observed after two weeks for all treatment groups. These mean percent reductions were most pronounced for the placebo group (7.57%), followed by pravastatin (3.96%). For BIBB, the reductions decreased with increasing dose, and were smallest for the highest BIBB dose group: 3.08% for 0.25mg, 2.45% for 0.50mg, and 0.87% for 1mg. The comparison between the 1mg BIBB treatment group and placebo was the only significant group comparison for this endpoint (p=0.0475).

For triglycerides, a nonparametric evaluation of median percent changes from baseline appeared to be more appropriate than the planned parametric evaluation of means. Median percent reductions from baseline were observed after two weeks for all treatment groups: 8.74% for the lowest BIBB dose group (0.25mg), 13.12% for the medium dose group (0.50mg), and 20.09% for the highest dose group (1mg), i.e. median percent reductions appeared to be dose-dependent. In comparison, median percent reductions of 2.99% were observed for placebo, and 13.59% for pravastatin. The only significant nonparametric comparison was the comparison between the 1mg dose group of BIBB and placebo (p=0.045).

There was no evidence for treatment effects on lipoprotein (a), large HDL, large VLDL, and average LDL particle size.

No association of larger lipid reductions with larger MES parameter values could be demonstrated. Similarly, no relevant correlations were observed between pharmacokinetic parameters and lipid reductions as well as MES parameters.

MES plasma concentrations for all BIBB 1464 MS treatment groups compared to placebo were clearly increased in a dose-dependent manner.

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A 14 day treatment with BIBB 1464 MS resulted in MES trough plasma concentrations that were probably close to a steady state level. MES plasma concentrations were still elevated 2 weeks after the last drug administration in all treatment groups. All MES derived parameters considered (MES Cmax, MES AUD, MES Ctrough) increased with the dose of BIBB 1464 MS and did not reach a plateau. This fact likely indicates that oxidosqualene cyclase was incompletely inhibited at steady state and, therefore, the maximally possible pharmacodynamic effect of BIBB 1464 MS was not seen in this study.

While there is a lack of predictability from single dose to steady state pharmacokinetics, after 2 weeks of dosing the data at steady state is predictable for each dose group. For the AUC at steady state, the expected increase with doubled dose was estimated as 1.95 (95% confidence interval [1.82, 2.07]). Likewise, for trough concentrations at steady state, the expected increase with doubled dose was estimated as 1.99 (95% confidence interval [1.88 , 2.10]).

Safety results:

The population considered in the evaluation of safety consisted of all 100 subjects that had been treated in the trial (20 subjects per treatment group), including the subjects who had received a threefold loading dose on study day 1 (two subjects in each BIBB 1464 MS treatment group).

As the most important safety result, the evaluation of eye lens opacification measures did not suggest any kind of cataractogenic treatment effect. This analysis included subjective LOCS III gradings as well as objective measures obtained by computer based evaluation of digital images taken of the eye lens. No individual clinically meaningful increases in eye lens opacification or density were observed.

An increased overall incidence rate of adverse events compared to placebo was observed only for the medium dose group of 0.50mg BIBB 1464 MS (80% compared to 50% for placebo), but not for the lowest dose of 0.25mg (35%) and the highest dose of 1.0mg (50%); the corresponding rate for the pravastatin reference group was 45%. The comparison between the medium dose group and placebo was not significant (p=0.096).

Headache was clearly the most frequent adverse event that occurred in the study. Headache incidence rates were elevated compared to placebo in the highest two BIBB 1464 MS dose groups (45% for 1.0mg, and 40% for 0.50mg, compared to 30% for placebo), but not for the lowest dose group of 0.25mg (15%), and not for pravastatin (15%). The slight, apparent trend towards dose dependency of headache incidence rates was not significant (p=0.1681). A similar trend was also observed for the incidence rates of drug related headache (p=0.1258).

Most of the reported adverse events were unspecific and all subjects recovered or the investigators considered follow-up as sufficient at the end of the study. No serious adverse events were reported, except for a hopitalisation for appendectomy which occurred in the placebo group. The large majority of adverse events was of mild to moderate intensity. Only five subjects (one subject in each treatment group) experienced events of severe intensity. Adverse events which were assessed as drug-related were reported for 14 subjects, headache and flatulence being the only of these events which occurred in more than one subject.

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There were three adverse events which called for particular attention. These were one case of skin rash which lead to treatment discontinuation, one case of severe alopecia that was associated with exceptionally high MES plasma concentrations, and a case of T-wave abnormality. The concerns about the latter case are considered as resolved after additional external examinations and review of pre-study ecg results.

Laboratory parameters, vital signs, ECG examinations, and general physical as well as ophthalmologic examinations did not give indication for a safety concern.

Conclusions:

Efficacy/Pharmacodynamics:

The trial clearly and robustly delivered proof of concept for the novel mechanism of action of BIBB 1464 MS in hyperlipemia. Based on this study, no conclusions can be drawn regarding the dose-response relationship or regarding the maximal therapeutic potential of the compound.

Safety:

Two week treatment with BIBB 1464 MS o.d. at doses up to 1.0mg, and with trough drug plasma concentrations limited by 3.5ng/mL, was safe in the present healthy male study population, especially with regard to alterations of the eye lens. In general, BIBB 1464 MS was well tolerated. Headache was the most frequent adverse event. Adverse events of particular importance were one case of skin rash in the 0.25mg dose group, and one case of alopecia in the 0.50mg dose group.

Pharmacokinetics:

While there is a lack of predictability from single dose to steady state pharmacokinetics, after 2 weeks of dosing the data at steady state is predictable for each dose group. Since this will be a chronically administered drug, this steady state predictability (dose proportionality) over therapeutic regimens from 0.25 to 1.0 mg per day is reassuring.