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 Pharma KG		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product:				
Name of active ingredient: Simvastatin Telmisartan		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 12 July 2000	**Number:** 502.341	**Study period (years):** 2000		

Title of study:	Pharmacokinetics of single oral doses of 40 mg simvastatin and its metabolite simvastatin acid with and without concomitant administration of telmisartan 80 mg daily, given orally over 6 days. A randomised, placebo controlled, double blind (for telmisartan), two way cross over trial in healthy subjects
Investigators:	[redacted]
Study center:	[redacted] Germany
Publication (reference):	n.a.
Clinical phase:	I
Objectives:	To assess the pharmacokinetics of simvastatin and simvastatin acid with/without concomitant administration of telmisartan

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Methodology:	Randomised, two way cross-over design, open-label for simvastatin, double blind for telmisartan
No. of subjects entered:	
total:	16 (8 male and 8 female)
each treatment:	16
Diagnosis and main criteria for inclusion:	Healthy female and male volunteers of 18-55 years old.
Test product:	Simvastatin and telmisartan
dose:	40 mg (simvastatin) and 80 mg (telmisartan)
mode of admin.:	Oral
batch no.:	906360 and 901855
Duration of treatment:	Telmisartan or placebo: 6 days simvastatin: one day (on day 6, concomitantly with telmisartan or placebo)
Reference therapy:	simvastatin and placebo
dose:	40 mg (simvastatin) and telmisartan placebo
mode of admin.:	Oral
batch no.:	906360 and 9980237
Criteria for evaluation:	
Efficacy/ Pharmacokinetics:	Timed plasma concentration determination of simvastatin and simvastatin acid following single dosing on day 6. $AUC_{0-\infty}$ (AUC_{0-tf}), C_{max} of simvastatin and simvastatin acid as primary endpoints. Secondary parameters: t_{max}, $t_{1/2}$, CL_{tot}/f, MRT_{tot}, V_z/f (simvastatin, simvastatin acid, telmisartan) and AUC_{ss} and $C_{max,ss}$ (telmisartan)
Safety:	Blood pressure, pulse rate, ECG, adverse events and laboratory tests, and physical examination
Statistical methods:	Descriptive statistics of secondary parameters, assessment of average bioequivalence with analysis of variance for simvastatin and simvastatin acid AUC and C_{max} treatment ratios, calculation of 90% confidence intervals for treatment ratios.

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SUMMARY - CONCLUSIONS:

Efficacy / Pharmacokinetics results:

The geometric mean concentration-time profiles of simvastatin following single dose oral administration of 40 mg simvastatin with and without telmisartan co-medication were nearly congruent. The geometric means of $AUC_{0-\infty}$ for 15 subjects were 38.50 ng*h/ml for treatment A (40 mg simvastatin, 80 mg telmisartan) and 38.02 ng*h/ml for treatment B (40 mg simvastatin, placebo). The figures for AUC_{0-tf} were 33.93 ng*h/ml for treatment A and 33.85 ng*h/ml for treatment B, respectively. The geometric means for Cmax were 9.90 ng/ml for treatment A and 10.54 ng/ml for treatment B, respectively.

The predetermined bioequivalence criteria (90% CI: 80-125%) were fulfilled for $AUC_{0-\infty}$ and AUC_{0-tf} with a geometric mean ratio of 101.74% and a CI of 85.69-120.81% and 100.67% (83.86-120.84%), respectively. The 90% confidence interval for C_{max} with 69.98-123.00% is outside the predetermined range.

The geometric mean concentration-time profiles of simvastatin acid following single dose administration of the 40 mg simvastatin with and without telmisartan co-medication were different for treatment A (40 mg simvastatin, 80 mg telmisartan) in comparison to treatment B (40 mg simvastatin, placebo). The C_{max} was increased and the $AUC_{0-\infty}$ was decreased. The geometric means of $AUC_{0-\infty}$ for 15 subjects were 15.61 ng*h/ml for treatment A (40 mg simvastatin, 80 mg telmisartan) and 17.95 ng*h/ml for treatment B (40 mg simvastatin, placebo). The figures for AUC_{0-tf} were 12.77 ng*h/ml for treatment A and 13.47 ng*h/ml for treatment B, respectively. The geometric means for C_{max} were 2.67 ng/ml for treatment A and 2.00 ng/ml for treatment B, respectively.

The predetermined bioequivalence criteria (90% CI: 80-125%) were not fulfilled for $AUC_{0-\infty}$ and AUC_{0-tf} with a geometric mean ratio of 88.03% and a CI of 73.71-105.13% and 95.26% (78.04-116.29%), respectively. The 90% confidence interval for C_{max} with 101.10-175.47% is outside the predetermined range.

Safety results:

Safety related laboratory investigation, evaluation of vital signs, ECG-parameter and physical examination did not reveal any clinically relevant findings for both treatments over the whole trial. The reported adverse events, related to the study medication, were already known for the treatment with telmisartan and were all assessed as mild.

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Conclusions:

Simvastatin and simvastatin acid plasma concentrations were determined by validated LC/MS and LC/MS/MS methods meeting the criteria for assay precision and accuracy.

Regarding the geometric mean concentration-time profiles of simvastatin following single dose administration with and without multiple dose telmisartan co-medication there is no evidence for a drug-drug interaction between telmisartan and simvastatin for the parent compound simvastatin. The two profiles are nearly congruent. Rate and extent of absorption are equivalent. The predetermined bioequivalence criteria (90% CI: 80-125%) are fulfilled for $AUC_{0-\infty}$ and AUC_{0-tf} with 85.69-120.81% and 83.86-120.84%, respectively. The 90% confidence interval for C_{max} with 69.98-123.00% is outside the predetermined range.

Regarding the geometric mean concentration-time profiles of simvastatin acid following single dose administration with and without multiple dose telmisartan co-medication there is an evidence for a drug-drug interaction between telmisartan and simvastatin for the metabolite simvastatin acid. The profile shows an increased maximum and an accelerated elimination resulting in a decrease of $AUC_{0-\infty}$. The predetermined bioequivalence criteria (90% CI: 80-125%) are not fulfilled for $AUC_{0-\infty}$ and AUC_{0-tf} with 73.71-105.13% and 78.04-116.29% respectively. The 90% confidence interval for C_{max} with 101.10-175.47% is outside the predetermined range.

In comparison to the published drug-drug interaction with simvastatin and CYP3A4 inhibitors like itraconazole, mibefradil, verapamil, erythromycin, grapefruit juice and others, which increase $AUC_{0-\infty}$ and C_{max} up to 10-15fold , the observed interaction for simvastatin with telmisartan is of no clinical significance. The minor decrease of geometric means of $AUC_{0-\infty}$ for simvastatin acid by 0.87 and the increase for geometric means of C_{max} by 1.34 is of no clinical relevance.

Overall, safety and tolerability, regarded under the condition of a clinical phase I study, could be assessed as good.