Boehringer Ingelheim

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**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2005-002851-41	
Name of active ingredient: Telmisartan and simvastatin		**Page:** **1 of 6**	**Synopsis No.:**
Ref. to Documentation:		**Volume:**	
Report date: 04 June 2008	**Trial No. / U No.:** 1228.1 / U08-1409-01	**Date of trial:** 06 Apr 2006 – 10 Aug 2007	**Date of revision** (if applicable)**:**

Title of trial:	Reduced factorial design, randomized, double-blind trial comparing combinations of telmisartan 20 or 80 mg and simvastatin 20 or 40 mg with single component therapies in the treatment of hypertension and dyslipidemia
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicentre Study, 122 sites in 13 countries
Publication (reference):	Data of this study has not yet been published
Clinical phase:	III
Objectives:	To demonstrate in patients with concomitant hypertension and dyslipidaemia: -Non-inferiority of telmisartan in combination with simvastatin compared with telmisartan alone with regard to blood pressure reduction -Non-inferiority of telmisartan in combination with simvastatin compared with simvastatin alone with regard to LDL-cholesterol reduction -Superiority of telmisartan in combination with simvastatin compared with simvastatin alone with regard to blood pressure reduction -Superiority of telmisartan in combination with simvastatin compared with telmisartan alone with regard to LDL-cholesterol reduction
Methodology:	Reduced factorial design, double blind, double dummy, randomised, international, multi-centre trial with 7 treatment arms and 8 weeks duration
No. of subjects:	
planned:	Enrolled: 2000 patients Entered: 1500 patients The planned numbers of patients per treatment group according to a reduced factorial design is detailed below:

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actual:	Enrolled: 2516 patients Entered: 1695 patients The actual numbers of patients per treatment group according to a reduced factorial design is detailed below:

Telmisartan (T) / Simvastatin (S)	S 0 mg	S 20 mg	S 40 mg
T 0 mg	-	125	125
T 20 mg	250	-	250
T 80 mg	250	250	250

Telmisartan (T) / simvastatin (S)	S 0 mg	S 20 mg	S 40 mg
T 0 mg	-	147	143
T 20 mg	283	-	276
T 80 mg	281	281	284

Diagnosis and main criteria for inclusion:	Male or female patients, age ≥18 years, with mild to moderate hypertension and hypercholesterolaemia
Test product:	
dose:	Telmisartan (T) and simvastatin (S) combinations given as individual components in the following doses (in mg) T80/S40, T80/S20, T20/S40 once daily in the evening.
mode of admin.:	Oral
batch no.:	B051001183 (T20); B051000788 (T80); B051001230, B061002129 (S20). For manufacture of S20 capsules, the following original batch nos. were used: 253467, 260215 (Zocor® 20 mg). Two S20 capsules were used for the S40 dose.
Reference therapy:	
dose:	Single component treatments (in mg): T80, T20, S40, and S20 given once daily in the evening.
mode of admin.:	Oral

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batch no.:	B051001183 (T20); B051001195 (T20 placebo); B051000788 (T80); B051001194 (T80 placebo); B051001230, B061002129 (S20); B051001227, B061002128 (S20 placebo). For manufacture of S20 capsules, the following original batch nos. were used: 253467, 260215 (Zocor® 20 mg); B051000624, B061002185 (T40 placebo used for manufacture of S20 placebo). Two S20 capsules were used for the S40 dose.
Duration of treatment:	8 weeks
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Mean diastolic blood pressure (DBP) determined by 24-hour ambulatory blood pressure measurement (ABPM) and LDL-cholesterol concentration. Secondary efficacy parameters included 24-hour ABPM measured mean systolic blood pressure (SBP), trough-to-peak ratio of DBP and SBP from ABPM, seated morning DBP and SBP, response to blood pressure (BP) treatment by categories, response to lipid lowering treatment, standard and extended lipid profile, and evaluation of metabolic parameters and biomarkers of potential CV risk.
Safety:	Monitoring for occurrence of adverse events, clinical laboratory parameters, pulse rate.
Statistical methods:	The primary endpoints were the changes from baseline to the end of trial (8 weeks) of 24-hour ABPM measured mean DBP and the percent change from baseline to the end of the trial of LDL-cholesterol concentrations. For the analysis of non-inferiority, the 2-sided 95% confidence intervals (CIs) for the difference of adjusted means between treatments were calculated. If the upper limit was less than 2 mmHg with respect to mean DBP and less than 6% with respect to LDL cholesterol, then non-inferiority was concluded and testing for superiority was performed. Confidence intervals were calculated based on ANCOVA models including baseline values as covariate and pooled countries and treatment as fixed effect.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:
Overall, the study population consisted of 55.2% males, and the mean age was 56.1 years, 78.4% of the patients were under 65 years of age. At baseline, mean diastolic blood pressure was 97.76 mmHg, and mean LDL-cholesterol was 162.04 mg/dL. The demographic and baseline parameters were similar in all treatment groups.

Primary endpoint
The primary endpoint analysis showed that the combined administration of telmisartan and simvastatin was non-inferior to telmisartan monotherapy in the reduction of DBP during the 24-hour ABPM dosing interval. The comparison between treatment reductions revealed a difference between adjusted means of −1.6 mmHg for T80/S40 vs. T80 (95%CI −2.6, −0.5), and −0.6 mmHg for T20/S40 vs. T20 (95%CI −1.7, 0.5). The upper limits of the 95% CIs were below the 2 mmHg margin; therefore, non-inferiority of the combination therapy was concluded for T20/S40 in comparison with T20, as well as for T80/S40 in comparison with T80. An additional reduction in the 24-hour mean DBP was observed with T80/S40 compared with T80 (−1.6 mmHg, $p<0.0001$). The primary endpoint analyses were supported by PPS analysis.
With regard to mean percentage change in LDL-cholesterol concentrations, the difference of adjusted means was 4.7% (95% CI 1.7, 7.7) between the T80/S40 and S40 treatments and 0.9% (95% CI −2.0, 3.9) between T80/S20 and S20 treatments. To conclude non-inferiority of the T/S combination to S monotherapy, the upper limit of the corresponding 2-sided 95% CI should have been below 6%. Therefore, the non-inferiority of the T80/S20 combination with respect to S20 monotherapy, but not for the T80/S40 combination with respect to S40 monotherapy was concluded with the selected non-inferiority margin. The primary endpoint analyses were supported by PPS analysis.

Secondary endpoints
The results of the analyses of the effect of T/S combination therapies and T and S monotherapies in BP were consistent with the findings of the primary endpoint analyses. In general, the treatment groups that had received T80 achieved better results than those which had received T20 with respect to blood pressure lowering. Likewise, the treatment groups that received combination therapy of telmisartan and simvastatin achieved better results than the treatment groups that had received telmisartan monotherapy. Overall, with respect to lipid lowering, the T/S combination therapies were slightly less effective than the respective S monotherapies.

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Safety results:

All patients treated with at least 1 dose of randomised medication were included in the safety analysis (treated set, n=1688). Adverse events (AEs) were recorded separately for screening, placebo run-in, randomised period, and post-treatment. From the 1688 patients, 400 patients (23.7%) experienced an AE during this trial. The frequency of patients with AEs was similar in all treatment groups, with the highest incidence in the simvastatin monotherapy groups (26.2%). The incidences of AEs at the system organ class and preferred term level were similar in all treatment groups. The majority of AEs were of mild or moderate intensity. In total, only 14 patients (0.8%) had AEs of severe intensity. AEs of severe intensity were present in every treatment group, ranging in frequency from 0.4% (T20, T80/S40, and T20/S40) to 2.1% (S20). Study drug-related AEs as assessed by the investigator occurred in 4.8% of the patients, with a slightly higher frequency in the S20 group (6.2%). Overall, based on system organ class, the most frequent events were infections and infestations (6.0%), nervous system disorders (5.0%), and musculoskeletal and connective tissue disorders (4.1%). At the preferred term level, the most frequent AEs were headache (3.3%) and nasopharyngitis (1.7%). The most frequently occurring AEs had a similar distribution across all treatment groups.
Only 2.6% of patients had an AE which led to the discontinuation of treatment, with proportions that ranged from 1.8% (T80) to 3.6% (S40). In the course of the trial, in total 13 patients experienced an SAE (0.8%) during treatment; with similar incidences in all treatment groups. None of the SAEs was considered drug-related by the investigator. In the course of the study a 70 year old male patient receiving T80 died. The cause of death was suspected acute myocardial infarction and was not considered study drug-related by the investigator.

Concerning vital signs and the physical examination there were no safety issues in any of the treatment groups.

In summary, the combined administration of the T/S combination did not lead to a notably higher incidence of AEs or of laboratory abnormalities than those observed in the T or S monotherapy groups.

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Conclusions: The combination of telmisartan/simvastatin was non-inferior to telmisartan monotherapy in the reduction of DBP during the 24-hour ABPM dosing interval. For the comparison between T/S and S in LDL cholesterol reduction, non-inferiority was concluded for T80/S20 with respect to S20, but not for T80/S40 with respect to S40 given the selected non-inferiority margin. The evaluation of safety yielded no unexpected results and the observed safety data was consistent with the safety profiles of telmisartan and simvastatin.