Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: MICARDIS®			
Name of active ingredient: Telmisartan		**Page 1 of 5**	
Report date: 06 JUL 2004	**Trial Number:** 502.392	**Study period (dates):** 09 OCT 02 - 30 NOV 03	**Date of Revision**

Title of study:	A Prospective, Randomised, Open-Label, Blinded-Endpoint, Parallel Group, Multicentre, Forced-Titration, 14-Week Treatment Study Comparing MICARDIS® (telmisartan 40-80-80 mg, QD) and ALTACE® (ramipril 2.5-5-10 mg, QD) in Patients with Mild-to-Moderate Hypertension using Ambulatory Blood Pressure Monitoring **PRISMA II** Study (**P**rospective **R**andomised **I**nvestigation of the **S**afety and Efficacy of **M**icardis® vs Ramipril using **A**BPM)
Investigator:	Multicentre study without official designation of a Principal or Coordinating Investigator
Study centers:	Multicentre study
Publication (reference):	See reference list
Clinical phase:	IV
Objectives:	The primary objective of this study was to demonstrate that telmisartan 80 mg is at least as effective and possibly superior to ramipril 5 mg and 10 mg in lowering mean ambulatory diastolic and systolic blood pressure during the last 6 hours of the 24-hour dosing interval in mild-to-moderate hypertensive patients at the end of an 8 and 14-week treatment phase, respectively.
Methodology:	Prospective, randomised, open-label, blinded-endpoint, parallel group, forced titration, comparison trial, using ABPM
No. of subjects: **planned:** **actual:**	 Entered: 750 Total entered/randomised: 812 Telmisartan 40-80-80 mg: 405 Ramipril 2.5-5-10 mg: 407
Diagnosis and main criteria for inclusion:	Patients age 18 years and older with mild-to-moderate hypertension defined as a mean seated DBP ≥95 mmHg and ≤109 mmHg and a 24-hour ABPM mean DBP ≥85 mmHg, each at baseline.
Test product:	MICARDIS® (telmisartan)

dose:	40 mg for two weeks, then forced titration to 80 mg for 12 weeks, once daily
mode of admin.:	Tablets, p.o.
batch no.:	
Duration of treatment:	14 weeks
Reference therapy:	ALTACE® (ramipril)
dose:	2.5 mg for two weeks, then forced titration to 5 mg for six weeks, then forced titration to 10 mg for six weeks, once daily.
mode of admin.:	Capsules, p.o.
batch no.:	
Criteria for evaluation:	
Efficacy:	Change from baseline in the last 6-hour mean DBP and SBP as measured by ABPM at the end of both an 8-week treatment period (i.e., telmisartan 80 mg vs. ramipril 5 mg) and a 14-week treatment period (i.e., telmisartan 80 mg vs. ramipril 10 mg).
Safety:	Adverse events, blood pressure and pulse rate monitoring were evaluated with screening of routine laboratory tests, and ECG for study qualification.
Statistical methods:	Analysis of covariance with treatment group and centre as main effects, and baseline as the covariate. Mantel-Haenszel test controlling for centres when evaluating categorical response variables; closed testing procedure to account for multiple primary comparisons.

SUMMARY – CONCLUSIONS:

Efficacy results:

Telmisartan 80 mg was found to be superior to both ramipril 5 mg and ramipril 10 mg in the change from baseline in the last 6 hour ABPM mean DBP and SBP. Telmisartan was also significantly superior to ramipril for each of the ABPM secondary endpoints: 24-hour mean, morning mean, daytime mean and nighttime mean, and DBP and SBP load.

Using a hierarchical closed testing procedure, non-inferiority of telmisartan 80 mg compared to ramipril 10 mg at the end of a 14-week treatment period was first shown analyzing the per-protocol analysis set (PP-ABPM-14W) with a two-sided 95% confidence interval on the difference between the adjusted mean changes in the last 6 hour ABPM mean DBP of -4.7, -2.1 mmHg. These results were confirmed when analyzing the full analysis set (FAS-ABPM-14W) (95% confidence interval of -4.7, -2.3 mmHg). Having found telmisartan 80 mg to be non-inferior to ramipril 10 mg, superiority testing was performed using the FAS-ABPM-14W analysis set. The adjusted mean reduction, as measured by the change from baseline in the last 6 hour ABPM mean, in DBP for telmisartan 80 mg (-8.4 mmHg) was significantly (p<0.0001) greater than that for ramipril 10 mg (-5.0 mmHg). For SBP, the adjusted mean reduction was also significantly (p<0.0001) greater for telmisartan 80 mg (-12.0 mmHg) compared to ramipril 10 mg (-7.3 mmHg).

Non-inferiority of telmisartan 80 mg compared to ramipril 5 mg at the end of an 8-week treatment period was then shown analyzing the per-protocol analysis set (PP-ABPM-8W) with a two-sided 95% confidence interval on the difference between the adjusted mean changes in the last 6-hour ABPM mean DBP of -4.4, -2.0 mmHg. These results were confirmed when analyzing the full analysis set (FAS-ABPM-8W) (95% confidence interval of -4.8, -2.6 mmHg). Having found telmisartan 80 mg to be non-inferior to ramipril 5 mg, superiority testing was performed using the FAS-ABPM-8W analysis set. The adjusted mean reduction, as measured by the change from baseline in the last 6-hour ABPM mean, in DBP for telmisartan 80 mg (-7.5 mmHg) was significantly (p<0.0001) greater than that for ramipril 5 mg (-3.8 mmHg). For SBP, the adjusted mean reduction was also significantly (p<0.0001) greater for telmisartan 80 mg (-10.7 mmHg) compared to ramipril 5 mg (-5.4 mmHg).

Strong support for these significant results for the primary endpoints in favour of telmisartan 80 mg compared to ramipril 5 mg and 10 mg were found when analyzing the secondary endpoints. The 24-hour mean profiles of the

reductions in both DBP and SBP hourly mean changes for telmisartan 80 mg were consistently greater than those for either ramipril 5 mg or ramipril 10 mg. Further, for each of the ABPM secondary endpoints relating to changes from baseline in BP (i.e., 24-hour mean, morning mean, daytime mean, nighttime mean, and DBP and SBP load) telmisartan 80 mg had significantly ($p<0.0001$) greater reductions than ramipril 5 mg and 10 mg. These resulted in rates of response for each of the three response variables related to the 24-hour mean being significantly ($p<0.01$) greater for telmisartan 80 mg compared to both ramipril 5 mg and 10 mg.

Results of the analyses comparing the changes from baseline in the in-clinic trough BPs also confirmed the results of the primary endpoints. There were significant differences found in favour of telmisartan 80 mg for both DBP and SBP when comparing the adjusted mean changes from baseline at the end of an 8 week treatment period (DBP: Telmisartan 80 mg -10.4 mmHg, Ramipril 5 mg -6.8 mmHg; $p<0.0001$, SBP: Telmisartan 80 mg -13.9 mmHg, Ramipril 5 mg -8.1 mmHg; $p<0.0001$) and when comparing the adjusted mean changes from baseline at the end of a 14-week treatment period (DBP: Telmisartan 80 mg -11.0 mmHg, Ramipril 10 mg -7.9 mmHg; $p<0.0001$, SBP: Telmisartan 80 mg -14.5 mmHg, Ramipril 10 mg -9.4 mmHg; $p<0.0001$). These changes resulted in response rates for each of the four response variables related to the in-clinic BPs being significantly ($p\leq0.02$) greater for telmisartan 80 mg compared to both ramipril 5 mg and 10 mg.

When analyzing the Health Related Quality of Life (HRQL) endpoints, no significant differences were found between telmisartan 80 mg and ramipril 5 mg or 10 mg.

Safety results:

This study confirmed the favourable safety profiles of both telmisartan and ramipril, with no major differences between the treatment groups. One or more adverse events were reported by 223 (27.5%) of randomised patients during active treatment. The majority of the AEs in each of the treatment groups were of mild or moderate intensity. Severe AEs were reported by 45 patients during the active treatment period, 15 patients who received telmisartan, 30 patients who received ramipril. A total of 32 (3.9%) randomised patients (10 telmisartan, and 22 ramipril) reported at least one non-serious adverse event that led to discontinuation from the study.

Only ten adverse events were reported in at least 2% of patients in any of the treatment groups. Cough was reported at an incidence of 1.5% and 10.1% of telmisartan and ramipril patients, respectively; headache was reported at an incidence of 6.7% and 8.1% of telmisartan and ramipril patients, respectively. All other AEs were reported with an incidence <5%. Only four drug-related AEs were identified at a rate of at least 1% (oedema peripheral, dizziness, headache, and cough). All of these AEs have been previously observed in clinical trials with these drugs and are listed as expected in their prescribing information. (R01-1019, R02-0164)

Twenty-two (22) patients reported an SAE during the course of the trial. None of the SAEs were considered to be drug-related.

Conclusions:

This study clearly demonstrates that telmisartan 80 mg is both safe and more effective than both ramipril 5 mg and ramipril 10 mg in controlling both DBP and SBP in hypertensive patients during the last six hours of the dosing interval, a measure of the early morning period when patients are at their greatest risk of life-threatening cardiovascular and cerebrovascular events. This finding along with strong evidence that telmisartan 80 mg results in better blood pressure control over the entire 24-hour dosing interval could indicate an advantage in reducing the occurrence of such cardiovascular and cerebrovascular events.