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Clinical Study Synopsis for Public Disclosure

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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..

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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 7**	
Report date: 30 APR 2004	**Trial Number:** 502.391	**Study period (dates):** 03 OCT 02 - 07 NOV 03	**Date of Revision** 03 NOV 2004

Title of study:	A Prospective Randomised Open- Label Blinded-Endpoint (PROBE) Trial Comparing Telmisartan (MICARDIS®) (40-80-80mg QD) and Ramipril (2.5-5--10mg QD) in Patients with Mild-to-Moderate Hypertension using Ambulatory Blood Pressure Monitoring **PRISMA** = **P**rospective **R**andomised **I**nvestigation of the **S**afety and Efficacy of **M**icardis® vs Ramipril using **A**BPM
Investigator:	[redacted]
Study centers:	Austria (6), France (7), Germany (9), Netherlands (9), South Africa (8), Spain (8), Switzerland (5), UK (21)
Publication (reference):	See reference list
Clinical phase:	IV
Objectives:	The primary objective of this study was to demonstrate that MICARDIS® (telmisartan 80mg) was at least as effective (and possibly superior to) ramipril 5mg and 10mg in lowering mean ambulatory diastolic blood pressure (DBP) and systolic blood pressure (SBP) during the last six hours of the 24-hour dosing interval in mild-to-moderate hypertensive patients at the end of an 8-and 14-week treatment period, respectively. Secondary objectives compared telmisartan (80mg) and ramipril (5mg and 10mg) on:1) the reduction in the last six-hour ABPM mean pulse pressure (PP) relative to dosing, 2) the reductions in the 24-hour ABPM mean DBP, SBP and PP relative to dosing, 3) reductions in ABPM mean DBP, SBP and PP during other periods of the 24-hour dosing interval (i.e. morning, daytime, and night-time) relative to clock-time, 4) change from baseline in systolic and DBP load during the 24-hour dosing interval, 5) reductions in the mean seated trough DBP and SBP measured using a manual in-clinic cuff sphygmomanometer, 6) responder rates as determined by both ABPM and manual in-clinic cuff measurements and 7) Health-Related Quality of Life (HRQL).
Methodology:	This was a Prospective, Randomised, Open-label, Blinded Endpoint (PROBE), forced titration, parallel group, comparison trial, using ABPM.
No. of subjects: **planned:**	entered: 780

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actual:	enrolled: 1593 Telmisartan (MICARDIS®) entered: 397 treated: 397 analysed (for primary endpoint): 296 (8 weeks) / 287 (14 weeks) Ramipril (TRITACE®) entered: 404 treated: 404 analysed (for primary endpoint): 307 (8 weeks) / 293 (14 weeks)
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 24-hr mean diastolic ambulatory blood pressure ≥ 85 mmHg.
Test product:	Telmisartan (MICARDIS®)
dose:	40mg for 2 weeks, then up titration to 80mg once daily
mode of admin.:	Tablets per os
batch no.:	40mg: 106505 80mg: 106380
Duration of treatment:	14 weeks
Reference therapy:	Ramipril (TRITACE®)
dose:	2.5mg for two weeks, then up titration to 5mg for six weeks then up titration to 10mg for six weeks, once-daily
mode of admin.:	Tablets p.o.
batch no.:	2.5mg: 40A407 5mg: 40A440 10mg: 1A438
Criteria for evaluation:	

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Efficacy:	Reduction in blood pressure during the last six hours of the 24-hour dosing interval as measured by ABPM in patients treated with telmisartan compared to patients treated with ramipril was analysed. Multiple dosage comparisons (i.e. telmisartan 80mg versus ramipril 5mg and ramipril 10mg after eight and 14 weeks of treatment, respectively) of the two primary endpoints (i.e. reduction in DBP and SBP during the last six hours of the 24-hour dosing interval as measured by ABPM) was performed using a completely hierarchical, closed testing procedure. Secondary analyses included comparisons of patients treated with telmisartan 80mg and patients treated with ramipril 5mg or 10mg at the end of an 8-week or 14-week treatment period, respectively, for the following endpoints:
	1. Changes from baseline in the last 6-hour ABPM mean (relative to dosing time) for PP, 2. Changes from baseline in the 24-hour ABPM mean (relative to dosing time) for DBP, SBP and PP. 3. Changes from baseline in the ABPM mean DBP, SBP and PP (relative to clock-time) during other periods (i.e. morning, daytime, night-time) of the 24-hour dosing interval. 4. Changes from baseline in systolic and DBP load during the 24-hour dosing interval. 5. Changes from baseline in mean trough seated DBP and SBP as determined by manual in-clinic cuff sphygmomanometer. 6. Percentage of patients responding as determined by both ABPM and manual in-clinic cuff blood pressures. 7. Changes from baseline in patient HRQL as measured by Psychological General Well-Being Index (PGWB).
Safety:	Evaluation of adverse events, pulse rate and cuff blood pressure monitoring.
Statistical methods:	In order to test the multiple hypotheses multiple dosage comparisons of the two primary endpoints were performed using a completely hierarchical, closed testing procedure. Hierarchical Closed Testing Procedure:

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Telmisartan 80mg compared to ramipril 5mg at the end of the 8-week treatment period in the reduction of BP during the last six hours of the 24-hour dosing interval:

- Non-inferiority DBP; if significant then,
- Superiority DBP, if significant then,
- Superiority SBP if significant then,

Telmisartan 80mg compared to ramipril 10mg at the end of the 14-week treatment period in the reduction of BP during the last six hours of the 24-hour dosing interval:

- Non-inferiority DBP; if significant then,
- Superiority DBP, if significant then,
- Superiority SBP if significant

Analysis of covariance with treatment and centre as main effects and baseline as a covariate; Mantel-Haenszel test controlling for centre.

SUMMARY – CONCLUSIONS:

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Efficacy results:

From the primary analysis, both in calculations using the per-protocol set and supported by using the FAS, telmisartan 80mg was found to be at least as effective as and also statistically significantly superior to ramipril 5mg in reducing the ABPM mean DBP in the last six hours of the dosing period. For both the FAS and per-protocol analysis the adjusted mean difference in DBP (telmisartan – ramipril) was -4.8mmHg ($p < 0.0001$). Similarly, telmisartan 80mg was found to be statistically significantly superior to ramipril 10mg in reducing the ABPM mean DBP in the last six hours of the dosing period ($p < 0.0001$); the adjusted mean difference in DBP (telmisartan – ramipril) was -3.0mmHg (per-protocol) and -2.7mmHg (full analysis set). Subsequent analysis of SBP showed a similar significant reduction in the last 6-hour ABPM in patients with telmisartan 80mg when compared to ramipril 5mg (adjusted mean difference -6.5mmHg) and 10mg (adjusted mean difference -3.7mmHg) ($p < 0.0001$).

Secondary analysis of these primary endpoints found no significant treatment by country interaction or by centre interaction.

For each of the secondary endpoints for both DBP and SBP telmisartan 80mg had significantly ($p < 0.05$) greater adjusted reductions than both the ramipril 5mg and 10mg groups. For PP there were significantly ($p < 0.05$) greater adjusted means in respect of last 6-hour mean, 24-hour mean, morning mean and night-time mean but no significant differences were found for daytime mean adjusted changes from baseline between telmisartan 80mg and ramipril 5mg and 10mg.

Telmisartan 80mg showed a significantly ($p < 0.0001$) greater reduction in both in clinic DBP and in clinic SBP when compared to ramipril 5mg, which in turn resulted in a significantly greater response rate ($p < 0.05$). Similar results were seen when telmisartan was compared to ramipril 10mg ($p = 0.0002$ for DBP and $p < 0.0001$ for SBP, response rate $p < 0.05$).

There was no statistically significant difference seen between the two treatments for any of the sub scales or the Global Index for the HRQL analysis. The length of the study (14 weeks) may have been insufficient to determine a significant difference in such a quality of life instrument.

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Safety results:

The mean duration of treatment was comparable across the groups. The overall incidence of AEs was low and rates were comparable across the groups. Overall, the study confirmed the favourable safety profile of all medications, with no major differences between treatment groups. One or more AEs were reported by 153 (38.5%) and 162 (40.1%) patients following telmisartan and ramipril respectively. The majority of the AEs in each of the treatment groups were of mild or moderate intensity. Severe AEs were reported by 13 patients who received telmisartan and 17 who received ramipril. A total of 4.6% randomised patients reported at least one non-serious AE that led to discontinuing the study.

Twenty three (23) AEs were reported by ≥ 1% of patients in any of the treatment groups, these were: abdominal pain, diarrhoea, dyspepsia, nausea, chest pain, fatigue, bronchitis, influenza, nasopharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, blood pressure increased, blood pressure systolic increased, arthralgia, back pain, dizziness (excl. vertigo), headache, depression, cough, dyspnoea, hyperhidrosis and hypertension. Cough, reported by patients taking ramipril was reported at an incidence of 6.7%, all other AEs were reported with an incidence of < 5%. Only four drug-related AEs were identified at a rate of ≥ 1% in any of the treatment groups, these were: fatigue, dizziness, headache and cough. All of these AEs have been previously observed in clinical trials with these products and are listed in their prescribing information.

Thirteen patients experienced a SAE during the study. For three of these patients, the SAE occurred prior to randomisation; none are documented after study completion. For ten others, the SAE occurred during the open-label treatment phase. Five of these patients were assigned to the telmisartan treatment group and five patients were assigned to the ramipril group. Overall, none of the SAEs were considered by the Investigators to be drug-related.

Conclusions:

Telmisartan is consistently more effective than ramipril in controlling blood pressure during the last six hours of the dosing interval, which is a measure of the early morning period when patients are at their greatest risk of life-threatening cardiovascular and cerebrovascular events.

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The safety profile of the two drugs was as expected for angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists. The principle difference being cough which is an acknowledged side effect of ACE inhibitor therapies.