Boehringer Ingelheim

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..

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 International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: Micardis®			
Name of active ingredient: Telmisartan		**Page: 1 of 3**	
Reporte date: 18 March 2003	**Trial-Number:** 502.316	**Study period (years):** 2002 - 2002	

Titel of Study:	A PROBE (Prospective, Randomised, Open-label, Blinded Endpoint) trial to investigate the efficacy and safety of telmisartan 40-80 mg once daily compared with losartan 50-100 mg once daily over a period of 12 weeks, and of telmisartan 80 mg + HCTZ 12.5 mg once daily compared with losartan 100 mg once daily + HCTZ 12.5 mg once daily over a period of further 12 weeks in mild to moderate hypertensive patients (grade 1 and grade 2 WHO-ISH guidelines 1999).
Investigator:	Coordinating Investigator: [redacted]
Study centres:	45 centres
Puplication (reference):	N/A
Clinical phase:	IV
Objectives:	**Efficacy: Primary objective:** To assess the efficacy of telmisartan 40-80 mg once daily compared with losartan 50-100 mg once daily in hypertensive patients evaluated by change from baseline in diastolic blood pressure (DBP) during the last 6 hours of the 24-hour dosing interval, at the end of the 12 weeks period of monotherapy treatment (ABPM). **Secondary objectives:** Changes from baseline in BP at the end of the monotherapy period of treatment and at the end of the study, evaluated by sphygmomanometric blood pressure measurement and ABPM. **Safety:** Incidence of adverse events (AE's); withdrawal due to adverse events; laboratory parameters
Methodology:	Open label (PROBE), randomised, parallel group comparison trial
No. of subjects:	Planned enrolled: 420 patients
total:	Randomized: 363
each treatment:	Telmisartan: 183; Losartan: 180
Diagnosis and main criteria for inclusion:	Essential hypertension: mild to moderate hypertension defined as mean diastolic blood pressure 95 and < 110 mmHg, and systolic blood pressure < 180 mmHg measured by manual cuff sphygmomanometer
Test product:	Telmisartan and Telmisartan + HCTZ
dose:	40 and 80 mg and 80 mg + 12.5 mg
mode of admin:	po

batch no.:	Telmisartan 902520 (40 mg), 902475 (80 mg); HCTZ (B9002)
Duration of treatment:	12 + 12 weeks treatment
Reference therapy:	Losartan and Losartan + HCTZ
dose:	50 mg and 100 mg and 100 mg + 12.5 mg
mode of admin.:	po
batch no.:	Losartan 990001, 992420, 995072, 994674, 205558 (50 mg), 990023, 990769, 994674, 202927, 203112 (100 mg); HCTZ (B9002)
Criteria for evaluation:	
Efficacy:	**Primary endpoint.** Change from baseline in diastolic blood pressure (DBP) during the last 6 hours of the 24-hour dosing interval, at the end of 12 weeks period of monotherapy treatment (ABPM) **Secondary endpoints.** **ABPM:** - change from baseline in DBP during the last 6 hours (ABPRM) of the 24 hour dosing interval at the end of the study (24 weeks); - change from baseline in SBP during the last 6 hours (ABPM) of the 24-hour dosing interval at 12 and 24 weeks; - changes from baseline DBP/SBP during the last 2 hours (ABPM) of the 24-hour dosing interval (trough BP) at 12 and 24 weeks; - changes from baseline of 24 hours mean SBP/DBP (ABPM) at 12 and 24 weeks; - comparison of DBP/SBP ABPM tracing profile at 12 and 24 weeks, analysed in blocks of 6 hours; - smoothness index at 12 and 24 weeks; - proportion of hypertensive patients (mean 24-hours ABPM values ≥130/80) at 12 and 24 weeks **Through cuff BP:** - changes from baseline in clinical DBP and SBP at 12 and 24 weeks, - number of responders (sitting DBP <90 mmHg and/or a fall ≥ 10 mmHg, sitting SBP <140 mmHg and/or a fall ≥ 10 mmHg) at 12 and 24 weeks; - number of controlled responders (sitting DBP <90 mmHg and sitting SBP <140 mmHg) at 12 and 24 weeks; - number of patients who reached normal BP (SBP <130 mmHg and DBP <85 mmHg); - withdrawal due to lack of efficacy
Safety:	Evaluation of adverse events, heart rate, physical examination, laboratory parameters, 12-lead ECG
Statistical methods:	Efficacy: intention-to-treat and explanatory analysis for primary endpoint and intention-to-treat for secondary endpoints; descriptive, analysis of

	variance/covariance, contingency tables, confidence intervals. Safety: descriptive statistics tabulation by system organ class
SUMMARY-CONCLUSION:	
Efficacy results:	Telmisartan obtained better diastolic blood pressure control at the end of dosing period than losartan: in the 12-week ITT population the primary study endpoint, DBP change in the last 6 hours block of ABPM, was -4.5 mmHg vs. -2.7 mmHg ($p = 0.056$). This result is supported by analysis of the PP population ($P = 0.048$). In the ITT analysis of secondary endpoints, a significant between-treatment difference was observed for change in blocks of 6 hours for DBP (ITT 12 weeks, $p = 0.040$). The average change in mean 24-hour DBP was -6.5 mmHg for telmisartan and -5.1 mmHg for losartan ($p = 0.079$). At 24 weeks, when 18.6% and 18.8% of patients, assigned to telmisartan or losartan respectively, had received HCTZ in addition, further 2-3 mmHg blood pressure reductions were observed with respect to end of monotherapy treatment period. The proportion of subjects who achieved normal BP values by ABPM criteria was higher on telmisartan than on losartan, both at 12 (39.7% vs. 36.3%) and at 24 weeks (49.4% vs. 42.7%). Clinically meaningful reductions in clinical DBP and SBP were observed in the range -12.7 mmHg to -14.5 mmHg/ -17.0 mmHg to -19.6 mmHg for telmisartan and -12.3 mmHg to -15.1 mmHg/-17.4 mmHg to -19.9 mmHg for losartan. The proportion of responders and controlled responders was similar in the telmisartan and in the losartan group and increased from the monotherapy phase (76% vs. 78.2% and 64.3% vs. 64.9%) with addition of HCTZ (89.4% vs. 87% and 73.1% vs. 70.8%).
Safety results:	The global incidence of adverse events was comparable in both treatment regimens (telmisartan 20.9%, losartan 20.6%). Addition of HCTZ resulted in a higher frequency of AE in the losartan (14.7%) than in the telmisartan regimen (2.9%). The incidence of AE of severe intensity was similary low (1.1% and 0.6%). The drop out rate for AE was 2.1% for telmisartan and 2.8% for losartan. The incidence rate of AE that were considered by the Investigator related to drug treatment was lower (2.7%) on telmisartan than on losartan (3.0%). The incidence of serious AE was 1.6% on telmisartan and 1.1% on losartan. No patient discontinues treatment due to laboratory AEs and no relevant changes were observed in median laboratory values. New physical findings occurred in a few patients only: 0.6% on telmisartan and 1.2% on losartan. New or worsening ECG changes were observed in 0.6% of cases in both groups.
Conclusions:	This 24-week study demonstrates that telmisartan is superior to losartan in obtaining blood pressure control throughout the 24-hour dosing interval and has a comparable safety profile on long term monotherapy. Telmisartan was better tolerated than losartan in addition with HCTZ.