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..

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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 6**	
Report date: 27 FEB 2007	**Number:** 502.397	**Study period (dates):** 09 JUL 03 to 01 JUN 06	**Date of Revision**

Title of study:	**A** prospective, randomised, double-blind, double-dummy, forced-titration, multicentre, parallel group, one year treatment trial to compare MICARDIS® (tel**mi**sartan) 80 mg versus COZAAR® (los**a**rtan) 100 mg, in hypertensive type 2 **d**iab**e**tic patients with **o**vert nephropathy (**AMADEO** Study)
Investigator:	[redacted] MD
Study centers:	Multi-centre study, 124 sites in 10 countries
Publication (reference):	Data from this study has not been published.
Clinical phase:	IV
Objectives:	The primary objective of this study was to show that telmisartan 80 mg is at least as effective (i.e. not inferior) and possibly superior to losartan 100 mg in reducing proteinuria (protein:creatinine ratio measured in spot urine) after one year of treatment in hypertensive patients with type 2 diabetes and overt nephropathy.
Methodology:	Prospective, randomised, double-blind, double-dummy, forced-titration, multi-centre, parallel-group comparison.
No. of subjects:	
planned:	entered: 800 patients
actual:	enrolled: 1567 entered: 860 Telmisartan: entered: 419 treated: 419 Losartan: entered: 441 treated: 441

Diagnosis and main criteria for inclusion:	Male and female patients aged 21 to 80 years with type 2 diabetes mellitus, with hypertension at screening defined as a) an average cuff systolic blood pressure (SBP) >130 mmHg and/or diastolic blood pressure (DBP) >80 mmHg in untreated patients, or b) patients receiving antihypertensive therapy (i.e. medications specifically prescribed to treat hypertension), and with overt nephropathy defined as urinary protein/creatinine ratio ≥700 mg/g (measured in spot urine) and serum creatinine ≤265 µmol/L (≤3.0 mg/dL) in women and ≤283 µmol/L (≤3.2 mg/dL) in men.
Test product:	Telmisartan (Micardis®)
dose:	40 mg with forced titration to 80 mg after 2 weeks, once daily
mode of admin.:	Oral (tablets)
batch no.:	PD-2285, PD-2325 (placebo run-in)
	PD-2287, PD-2500 (40 mg placebo); PD-2286, 2501 (40 mg)
	PD-2289, PD-2502 (80 mg placebo); PD-2288, PD-2503 (80 mg)
Duration of treatment:	1 year
Reference therapy:	Losartan (Cozaar®)
dose:	50 mg with forced titration to 100 mg after 2 weeks, once daily
mode of admin.:	Oral (over-encapsulated tablets)
batch no.:	PD-2285, PD-2325 (placebo run-in)
	PD-2296, PD-2407, PD-2468, PD-2469 (50 mg placebo and 100 mg placebo)
	PD-2310, PD-2332, PD-2339, PD-2390, PD-2471 (50 mg)
	PD-2293, PD-2311, PD-2340, PD-2388, PD-2391, PD-2394 (100 mg)

Criteria for evaluation:

Efficacy:

The primary endpoint was the change from baseline (Visit 6) in proteinuria [protein:creatinine ratio, urine protein to creatinine ratio, (UPCR) measured in spot urine] after one year of treatment with telmisartan 80 mg versus losartan 100 mg.

The secondary endpoints, measured after one year of treatment, were based on:

- Change from baseline in glomerular filtration rate [GFR, abbreviated Modification of Diet in Renal Disease (MDRD)]
- Change from baseline in serum creatinine
- Change from baseline in macroalbuminuria [albumin:creatinine ratio, Urine albumin to creatinine ratio, (UACR) measured in spot urine]
- Change from baseline in sodium excretion [sodium:creatinine ratio, Urine sodium to creatining ratio, (UNACR) measured in spot urine]
- Change from baseline in high sensitive C-reactive protein (CRP)
- Change from baseline in serum aldosterone
- Composite of a doubling of serum creatinine concentration (defined as the first serum creatinine value that was twice the baseline value, to be confirmed by a second creatinine value to be obtained at the next study visit which should be at least four weeks after the initial doubling), end stage renal disease (ESRD) (defined by the need for long-term dialysis, renal transplantation, or a serum creatinine > 6.0 mg/dL, i.e. ≥ 530 µmol/L), or all cause death
- Composite of morbidity and mortality from cardiovascular causes (myocardial infarction, stroke, first hospitalisation for heart failure, unstable angina, or coronary or peripheral revascularisation)

The secondary endpoints measured after eight weeks following one year of study treatment in the follow-up period:

- Time course of change in renal endpoints over eight weeks (UPCR, UACR, and UNACR) following discontinuation of study treatment

Safety:

Evaluation of adverse events. Measurement of changes from baseline in physical examinations, laboratory parameters and vital signs (mean SBP, mean DBP and pulse rate).

Statistical methods:

Analysis of covariance with treatment and centre as main effects and baseline as a covariate; time-to-event data were analysed using Kaplan-Meier methodology with treatment groups compared using the log-rank test.

SUMMARY – CONCLUSIONS:

Efficacy results:

The study population was predominantly males (61.1%), Caucasians (47.1%), with a mean age of 60.3 years and mean body mass index of 30.0 kg/m^2. On average, the patients had hypertension for 9.3 years, type 2 diabetes for 14.3 years, and diabetic nephropathy for 2.5 years. Baseline UPCR was 1991 mg/g (gMean), while UACR was 1394 mg/g (gMean). Mean blood pressure at baseline was 143.9 mmHg (SBP) and 79.6 mmHg (DBP) with a mean HbA1c at baseline of 7.9%. The treatment groups were well balanced with regard to all baseline parameters.

The primary endpoint analysis using the per-protocol analysis set showed that telmisartan was non-inferior to losartan with regard to the reduction of UPCR (mg/g) after one year of treatment. Using the full analysis set, UPCR was reduced by 29% for patients treated with telmisartan compared to 20% for patients treated with losartan. This treatment difference of reduction in UPCR for patients treated with telmisartan compared to patients treated with losartan was statistically significant (p=0.0284) indicating the superiority of telmisartan in reducing UPCR compared to losartan. Additional analysis found no significant treatment-by-time interaction indicating that the treatment differences were consistent throughout the one year treatment period.

Subgroup analyses to evaluate any effects on the changes in UPCR due to age, gender, race, pre-treatment with angiotensin receptor blockers (ARBs) and/or angiotensin converting enzyme inhibitors (ACE-Is), and last on treatment systolic blood pressure (SBP) and HbA1c tertiles, showed no significant treatment-by-subgroup interactions. For subgroups of last on treatment diastolic blood pressure (DBP) tertiles some evidence was found to suggest that treatment with telmisartan resulted in greater reductions in UPCR than treatment with losartan for patients with lower DBP at the end of treatment.

Efficacy results: (continued)	When evaluating the secondary efficacy endpoint of changes from baseline in UACR, treatment with both telmisartan and losartan resulted in significant ($p \leq 0.05$) reductions with the reduction for telmisartan patients significantly ($p=0.0451$) greater than the reduction for losartan patients. No significant difference was found between the increases for both treatment groups in serum creatinine. Changes from baseline in SBP and DBP, showed no significant differences between the two treatment groups. When evaluating the two composite time-to-event endpoints, no significant ($p=0.083$) difference was observed in the time to first event for the composite of a doubling of serum creatinine, ESRD, or all-cause death. For the composite of morbidity or mortality from cardiovascular causes treatment with telmisartan was found to significantly ($p=0.037$) prolong the time to first event compared to treatment with losartan. During the follow-up period, no evidence was found for any persistent pro-renal effects for treatment with either telmisartan or losartan. For both of the endpoints of UPCR and UACR the increases from last value on treatment for patients that had been treated with telmisartan were significantly ($p=0.0079$ and $p=0.0092$, respectively) greater than patients that had been treated with losartan.
Safety results:	The mean duration of treatment was 329.5 days for patients treated with telmisartan and 319.0 days for patients treated with losartan. Adverse events occurred in 83.0% of patients and were equally balanced between treatment groups. The evaluation of safety yielded results consistent with the known safety profiles of telmisartan and losartan and in accordance with the expectations for this study population suffering from hypertension, type 2 diabetes, and overt nephropathy. There were no unexpected safety concerns during the active treatment and follow-up periods of the trial. Study treatments were well tolerated.

Conclusions:

The results of this study confirmed the treatment benefit of telmisartan 80 mg in the treatment of hypertensive patients with type 2 diabetes and overt nephropathy in decreasing proteinuria as measured in spot urine after one year of treatment. Additionally the results established the superiority of telmisartan 80 mg compared to losartan 100 mg, a therapeutic agent approved by several regulatory authorities for treatment of diabetic nephropathy. These findings were further supported by the results of reductions in albuminuria and the results of the time-to-event composite endpoint of morbidity or mortality from cardiovascular causes. However, no persistent pro-renal effects were found following discontinuation of treatment with either telmisartan or losartan. These findings provide strong support for the continuous use of telmisartan for slowing down the progression to ESRD.