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..

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		Trial Synopsis	
Name of finished product: MICARDIS PLUS®			
Name of active ingredient: Telmisartan + hydrochlorothiazide		**Page 1 of 6**	
Report date: 12 NOV 04	**Trial Number:** 502.400	**Study period (dates):** 02 DEC 02 - 23 MAR 04	**Date of Revision**

Title of study:	A comparison of telmisartan 80 mg + hydrochlorothiazide 12.5 mg with amlodipine 10 mg + hydrochlorothiazide 12.5 mg in the control of blood pressure in older patients with predominantly systolic hypertension. A prospective, randomised, open-label, blinded end-point evaluation. (ATHOS study)
Investigator:	Multiple investigators: general practitioners, cardiologists, geriatricians and hypertension clinics. Principal investigator: [redacted] MD, [redacted] Denmark.
Study centres:	International, multicentre: Belgium (4), Denmark (12), Finland (6), France (5), Germany (23), Ireland (13), Italy (6), Netherlands (10), South Africa (5), Spain(5)
Publication (reference):	None
Clinical phase:	IV
Objectives:	The primary objective of this study was to demonstrate that telmisartan 80 mg + hydrochlorothiazide (HCTZ) 12.5 mg was not inferior (and possibly superior to) amlodipine 10 mg + HCTZ 12.5 mg in reducing ambulatory systolic blood pressure (SBP) in the last 6 hours of the 24-hour dosing interval (determined by ambulatory blood pressure monitoring: ABPM) in elderly patients with predominantly systolic hypertension. Secondary objectives included comparison of the effects of telmisartan 80 mg + HCTZ 12.5 mg with amlodipine 10 mg + HCTZ 12.5 mg and a comparison of the effects of telmisartan 80 mg with amlodipine 10 mg on (1) reduction in last 6-hour ABPM mean diastolic blood pressure (DBP) and pulse pressure (PP) (2) reduction in 24-hour ABPM mean, daytime ABPM mean, morning ABPM mean and night-time ABPM mean SBP, DBP and PP (3) reduction in trough SBP and DBP (4) health-related quality of life and (5) the proportion of patients achieving SBP response, SBP control, normal blood pressure and high normal blood pressure. In addition, the effects of telmisartan 80 mg monotherapy (i.e. before addition of HCTZ) on these parameters (and on reduction of ambulatory SBP in the last 6 hours of the dosing interval) were assessed after eight weeks and compared with amlodipine 10 mg monotherapy.

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Methodology:	Prospective, randomised, open-label, blinded end-point, forced titration, parallel group comparison, using ambulatory blood pressure monitoring (ABPM).
No. of subjects:	
planned:	entered: 850
actual:	enrolled: 1,265 Telmisartan 40mg/80mg/80mg + 12.5 mg hydrochlorothiazide: entered: 497 treated: 497 analysed (for primary endpoint): 448 Amlodipine 5mg/10mg/10mg + 12.5 mg hydrochlorothiazide: entered: 503 treated: 503 analysed (for primary endpoint): 424
Diagnosis and main criteria for inclusion:	Aged at least 60 years. Systolic blood pressure greater than 140 mmHg and diastolic blood pressure up to 95 mmHg. 24-hour mean systolic blood pressure measured by ABPM greater than 125 mmHg. Willing to give written informed consent.
Test product:	Telmisartan and hydrochlorothiazide
dose:	40 mg telmisartan for 2 weeks, then uptitration to telmisartan 80 mg for six weeks, then uptitration to telmisartan 80 mg + HCTZ 12.5 mg for six weeks
mode of admin.:	oral tablets
batch no.:	Telmisartan: 106505. Hydrochlorothiazide: F5074.
Duration of treatment:	Placebo run-in phase for two to four weeks followed by fourteen weeks randomised treatment phase.
Reference therapy:	Amlodipine and hydrochlorothiazide
dose:	5 mg amlodipine for 2 weeks, then uptitration to amlodipine 10 mg for six weeks, then uptitration to amlodipine 10 mg + HCTZ 12.5 mg for six weeks
mode of admin.:	oral tablets
batch no.:	Amlodipine: 2101110. Hydrochlorothiazide: F5074.

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Criteria for evaluation:	
Efficacy:	Reduction in SBP during the last six hours of the 24-hour dosing interval as measured by ABPM in patients treated with telmisartan 80 mg + HCTZ 12.5 mg compared to patients treated with amlodipine 10 mg + HCTZ 12.5 mg (at the end of the 14-week treatment period) was analysed. Secondary analyses included comparison of the effects of telmisartan 80 mg + HCTZ 12.5 mg and amlodipine 10 mg + HCTZ 12.5 mg (at the end of the 14-week treatment period) and comparison of telmisartan 80 mg and amlodipine 10 mg + HCTZ 12.5 mg (after 8 weeks of treatment) on (1) reduction in last 6-hour ABPM mean DBP and PP (2) reduction in 24-hour ABPM mean, daytime ABPM mean, morning ABPM mean and night-time ABPM mean SBP, DBP and PP (3) reduction in trough SBP and DBP (4) health-related quality of life assessed by the Psychological Well-Being Index (PGWB) and (5) the proportion of patients achieving SBP response, SBP control normal blood pressure and high normal blood pressure. The effects of telmisartan 80 mg on reduction of ambulatory SBP in the last 6 hours of the dosing interval was also compared with amlodipine 10 mg.
Safety:	Evaluation of adverse events and vital signs.
Statistical methods:	In order to test the multiple hypotheses analysis of the primary endpoint was performed using a completely hierarchical, closed testing procedure as follows: Telmisartan 80 mg + HCTZ 12.5 mg compared to amlodipine 10 mg + HCTZ 12.5 mg at the end of the 14-week treatment period for reduction of SBP in the last six hours of the 24-hour dosing interval: • non-inferiority regarding SBP at a pre-specified non-inferiority margin of 3 mmHg, if significant then, • superiority regarding SBP. Analysis of covariance with treatment and centre as main effects and baseline as a covariate when evaluating changes from baseline; Mantel-Haenszel test controlling for centre when evaluating categorical response variables.
SUMMARY – CONCLUSIONS:	

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Efficacy results:

In the primary analysis (of both the per-protocol and full analysis datasets) telmisartan 80 mg + HCTZ 12.5 mg was demonstrated to be at least as effective as amlodipine 10 mg + HCTZ 12.5 mg in reducing ABPM mean SBP in the last 6 hours of the dosing interval. The effect of telmisartan 80 mg + HCTZ 12.5 mg was not shown to be superior to amlodipine 10 mg + HCTZ 12.5 mg.

The adjusted mean change from baseline SBP in the last 6 hours was -18.8 mmHg in the telmisartan 80 mg/HCTZ 12.5 mg group and -17.7 mmHg in the amlodipine 10 mg/HCTZ 12.5 mg group (Per-Protocol analysis). The adjusted mean difference (telmisartan-amlodipine) was -1.1 mmHg (95% confidence interval -2.7, 0.5 mmHg; $p = 0.1655$).

Secondary analysis of the primary endpoint found no significant age interaction, gender effect or treatment-by-country interaction or treatment-by-centre interaction.

Analysis of other ABPM endpoints showed a significantly greater reduction in last 6-hour mean DBP, night-time mean DBP, 24-hour mean SBP and DBP, morning mean SBP and DBP and daytime mean SBP and DBP for telmisartan 80 mg + HCTZ 12.5 mg compared with amlodipine 10 mg + HCTZ 12.5 mg. There was no significant difference between these treatments on the effect on night-time mean SBP, PP in any endpoint time period, trough SBP and DBP measured in the clinic or health-related quality of life (assessed by PGWB).

The proportion of patients achieving SBP control at 14 weeks (defined as 24-hour mean SBP < 130 mmHg) was higher in the telmisartan 80 mg + HCTZ 12.5 mg group compared with the amlodipine 10 mg + HCTZ 12.5 mg (65.9% versus 58.3% respectively; $p = 0.0175$).

Comparison of the effects of telmisartan 80 mg monotherapy with amlodipine 10 mg monotherapy at eight weeks showed a significantly greater reduction in ABPM last 6-hour mean, night-time mean, 24-hour mean, morning mean and daytime mean SBP, DBP and PP and greater reduction in trough SBP and DBP in the amlodipine treatment group. However, there was no significant difference in the proportion of patients achieving SBP control at eight weeks (43.8% in the telmisartan 80 mg group versus 50.7% in the amlodipine 10 mg group). The increase in the General Health sub-scale of the PGWB index was significantly greater in the telmisartan 80 mg monotherapy group at eight weeks.

Safety results:

The mean treatment exposure was 95.5 days for the telmisartan group and 92.4 days for the amlodipine group. The observed adverse events were consistent with the prescribing information for telmisartan, amlodipine and HCTZ. The proportions of patients with adverse events ($p < 0.0001$), drug-related adverse events ($p < 0.0001$) and significant adverse events ($p < 0.0001$) were significantly greater in the amlodipine group compared with the telmisartan group.

At least one adverse event was reported by 205 patients (41.2%) in the telmisartan group compared with 270 patients (53.7%) in the amlodipine group. The majority of adverse events were of mild to moderate intensity. Peripheral oedema was the most common adverse event and was reported in 6 patients (1.2%) in the telmisartan group compared with 122 patients (24.3%) in the amlodipine group. The incidence of peripheral oedema was significantly greater in the amlodipine group ($p < 0.0001$).

Eighteen types of adverse event were reported with an incidence of at least 1% in either treatment group. These consisted of vertigo, diarrhoea, nausea, oedema, peripheral oedema, bronchitis, influenza, nasopharyngitis, urinary tract infection, contusion, arthralgia, back pain, dizziness, headache, sciatica, depression, cough and flushing. The incidence of all other reported adverse events was less than 5%.

Five types of drug-related adverse event were reported with an incidence of at least 1% in either treatment group. These consisted of oedema, peripheral oedema, dizziness, headache and flushing.

Thirty-seven patients experienced a serious adverse event. In twelve of these patients the event occurred during the placebo run-in phase. Twenty-four patients experienced a serious adverse event during the randomised treatment phase (11 in the telmisartan group and 13 in the amlodipine group). Two of these events (hypertensive crisis in 1 patient and hypotension resulting in low back contusion in 1 patient) were reported as related to telmisartan and one event (confusional state in 1 patient) was reported as related to amlodipine. One patient (in the amlodipine group) had a fatal myocardial infarction after completing study treatment. Two patients in the telmisartan group died (pancreatitis: 1 patient; unknown cause: 1 patient). None of the fatal serious adverse events were considered to be drug-related.

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Conclusions:

Telmisartan 80 mg/HCTZ 12.5 mg is not inferior to amlodipine 10mg/12.5 mg in reducing the ambulatory SBP in the last six hours of the 24-hour dosing interval in older patients with predominantly systolic hypertension. (However, telmisartan 80 mg/HCTZ 12.5 mg could not be shown to be superior to amlodipine 10mg/HCTZ 12.5 mg.)

Telmisartan 80 mg/HCTZ 12.5 mg results in significantly greater reductions in ambulatory blood pressures in all other time intervals (24-hour mean SBP and DBP, last 6-hour mean DBP, night-time mean DBP, morning mean SBP and DBP and daytime mean SBP and DBP) compared with amlodipine 10 mg/HCTZ 12.5 mg (apart from SBP at night-time where there was no difference between the two treatments). There is no difference between the two treatments in their effect on PP. The proportion of patients achieving SBP control is significantly higher after telmisartan 80 mg/HCTZ 12.5 compared with after amlodipine 10mg/HCTZ 12.5 mg. There was no significant difference between the effects of the treatments on trough SBP and DBP measured in the clinic or health-related quality of life (assessed by PGWB).

Analysis of the efficacy data at eight weeks suggests that amlodipine 10 mg monotherapy is superior to telmisartan 80 mg monotherapy in reducing ambulatory blood pressures in older patients with predominantly systolic hypertension but the proportion of patients achieving SBP control is still low in both treatment groups. However, these findings must be interpreted with caution as the significantly higher rate of withdrawal due to adverse events in the amlodipine group may have biased the efficacy analysis in favour of amlodipine.

The safety profile of the study treatments was consistent with their prescribing information. Telmisartan is better tolerated than amlodipine. There were significantly fewer adverse events, drug-related adverse events and significant adverse events in the telmisartan treatment group compared with the amlodipine group.