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® HCT			
Name of active ingredient: telmisartan and hydrochlorothiazide		**Page 1 of 5**	
Report date: 09 MAR 2007	**Trial-Number:** 502.476	**Study period (dates):** 14 SEPT 05 to 27 JUN 06	**Date of Revision**

Title of study:	A randomized, double-blind, placebo-controlled, forced-titration, Phase IV study comparing telmisartan 80 mg + hydrochlorothiazide 25 mg versus valsartan 160 mg + hydrochlorothiazide 25 mg taken orally for eight weeks in patients with Stage 1 or Stage 2 hypertension
Investigator:	[redacted] M.D. (Coordinating Investigator)
Study centers:	Multicentre study (approximately 125)
Publication (reference):	N/A
Clinical phase:	IV
Objectives:	The primary objective of this study was to show that telmisartan 80 mg + hydrochlorothiazide 25 mg was superior to placebo in lowering diastolic blood pressure (DBP) and systolic blood pressure (SBP), at least as effective as valsartan 160 mg + hydrochlorothiazide 25 mg in lowering DBP and possibly superior in lowering both DBP and SBP in patients with Stage 1 or Stage 2 hypertension.
Methodology:	Randomized, double-blinded, double-dummy, placebo-controlled, forced-titration, parallel group comparison using seated trough cuff blood pressure.
No. of subjects:	
planned:	Entered: 1125
actual:	Enrolled: 2322 Entered: 1185 Treatment A: Telmisartan 80 / HCT 25 mg entered: 529 treated: 528 analysed (for primary endpoint): 498 Treatment B: Valsartan 160 / HCT 25 mg entered: 524 treated: 523 analysed (for primary endpoint): 498 Treatment C: Placebo entered: 132 treated: 130 analysed (for primary endpoint): 119

Diagnosis and main criteria for inclusion:	Male and female patients ≥18 years of age with Stage 1 or Stage 2 hypertension defined as a baseline seated trough cuff DBP of ≥95 mmHg to ≤120 mmHg at baseline (Visit 2).
Test product:	Telmisartan plus HCTZ
dose:	80 / 25 mg
mode of admin.:	Oral Tablet
batch no.:	
Duration of treatment:	8 weeks
Reference therapy:	Valsartan plus HCTZ
dose:	160 / 25 mg
mode of admin.:	Oral tablet (over-encapsulated)
batch no.:	
Reference therapy:	Placebo
dose:	N/A
mode of admin.:	Oral tablets (matching MICARDIS® HCT) and Oral tablets over-encapsulated (matching over-encapsulated DIOVAN® HCT)
batch no.:	

Criteria for evaluation:

Efficacy:

Primary endpoints:

Change from baseline in mean seated trough cuff diastolic (DBP) and systolic blood pressure (SBP) at the end of an 8-week treatment period.

Hierarchical Closed Testing Procedure:

Superiority of telmisartan 80 mg plus HCTZ 25 mg compared to placebo at the end of the 8-week treatment period in the reduction of seated trough cuff DBP; if significant then,

Superiority of telmisartan 80 mg plus HCTZ 25 mg compared to placebo at the end of the 8-week treatment period in the reduction of seated trough cuff SBP; if significant then,

Non-inferiority of telmisartan 80 mg plus HCTZ 25 mg compared to valsartan 160 mg plus HCTZ 25 mg at the end of the 8-week treatment period in the reduction of seated trough cuff DBP; if significant

Superiority of telmisartan 80 mg plus HCTZ 25 mg compared to valsartan 160 mg plus HCTZ 25 mg at the end of the 8-week treatment period in the reduction of seated trough cuff SBP; if significant then,

Superiority of telmisartan 80 mg plus HCTZ 25 mg compared to valsartan 160 mg plus HCTZ 25 mg at the end of the 8-week treatment period in the reduction of seated trough cuff DBP.

Secondary endpoints:

Percentage of patients responding to treatment based on DBP and SBP.

Percentage of patients who discontinue due to uncontrolled hypertension defined as SBP ≥180 mmHg and/or DBP ≥120 mmHg.

Change from baseline (Visit 2) in mean seated cuff DBP and SBP at the one and three hour post dose time points following an 8-week treatment period.

Safety:

Safety was evaluated by:

- adverse events
- 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 as a main effect and baseline BP as a covariate; Mantel-Haenszel test

SUMMARY – CONCLUSIONS:

Efficacy results: For the primary endpoints of the change from baseline in the seated trough cuff DBP and SBP, telmisartan 80 / HCTZ 25 mg (T80/H25) was found to be superior to placebo (adjusted mean changes in seated trough cuff DBP and SBP of -18.2 and -24.6 mmHg, respectively, for T80/H25 compared to -6.1 and -4.1 mmHg, respectively, for placebo). As well, these changes from baseline for T80/H25 were statistically superior to those for valsartan 160 / HCTZ 25 mg (V160/H25) of -17.0 mmHg for DBP and -22.5 mmHg for SBP, with the adjusted mean differences being -1.2 mmHg for DBP (p=0.0254) and -2.1 mmHg for SBP (p=0.0174).

Secondary analysis on the primary endpoints of the changes from baseline in seated trough cuff DBP and SBP confirmed the overall significant treatment differences found in the primary analyses. No significant treatment-by-centre interaction was found when analyzing the changes from baseline in seated trough cuff DBP (p=0.5167) and SBP (p=0.5761). Further, the results of the analyses on the secondary endpoints of response rates for each of the four response criteria based on the seated trough cuff BPs found T80/H25 to have response rates that were significantly ($p<0.0001$) greater than placebo and also significantly greater ($p<0.005$) than V160/H25 in DBP control, DBP response, and SBP response.

From subgroup analyses on the primary endpoints (seated trough cuff DBP and SBP at the 8 week time point), no statistically significant treatment-by-subgroup interaction was found for age group (<65 years old or $\geq$65 years old), or stage of hypertension at baseline. Nor were there any statistically significant treatment by subgroup interactions found in seated trough cuff DBP for the subgroup of gender and for trough cuff SBP for the subgroup of race. There was however some evidence for a treatment-by-subgroup interaction for gender with regard to seated trough SBP and for race with regard to seated trough DBP which was not deemed to be qualitative in nature, but rather largely influenced by the results of the placebo treatment group.

The results of the one-hour and three-hour post dose sub-study found T80/H25 to be superior to V160/H25 for both DBP and SBP at the one-hour (p=0.0031 and 0.0021, respectively) and three-hour point (p=0.0043 and 0.0022, respectively).

Safety results: This study confirmed the favorable safety profile of both T80/H25 and V160/H25 as compared to placebo. The vast majority of AEs reported by patients were of mild or moderate intensity.

In total, one or more adverse event (regardless of drug relationship) was reported by 192 patients (36.47%) in the T80-T80/H25 arm, 191 (36.5%) in the V160-V160/H25 arm, and 55 patients (42.3%) in the placebo arm. A total of ten AEs were reported at an incidence of ≥2% in any treatment group: nasopharyngitis, sinusitis, upper respiratory tract infection, back pain, muscle spasm, dizziness, headache, anxiety, cough, hypertension.

A total of 126 (10.7%) patients reported a drug related AE during the randomization period. During the combination period, 45 (8.9%) patients in the T80-T80/H25 arm, 39 (7.8%) in the V160-V160/H25 arm, and 8 (6.2%) in the placebo arm reported drug related adverse events. A total of three AEs considered drug related were reported at an incidence of ≥1% in any treatment group: dizziness, headache, and fatigue. The overall incidence was similar across treatment groups with no event reported above the 3.0% level.

Ten patients reported SAEs during the active treatment phase (eight in the T80-T80/H25 arm and two in the V160-V160/H25 arm). All SAEs were considered non-drug related. Of two deaths reported during this study, neither were drug related; one reported during the placebo run-in and the other reported post-study

Treatment with both telmisartan and valsartan in combination with HCTZ did not lead to a significant percentage of patients experiencing changes in laboratory parameters compared to placebo.

Conclusions:

Both T80/H25 and V160/H25 were well tolerated and provided effective blood pressure control with acceptable safety profiles as compared to placebo. Furthermore, T80/H25 produced statistically greater reductions in both DBP and SBP mean seated trough cuff measurements compared to placebo and V160/H25. With the strong evidence available directly correlating blood pressure reductions to cardiovascular and cerebrovascular risk reduction, the additional efficacy afforded by T80/H25 over V160/H25 could confer to it an advantage in reducing risk of cardiovascular and cerebrovascular morbidity and mortality events.