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 ingredients: Telmisartan plus hydrochlorothiazide		**Page: 1 of 5**	
Report date: 09 JUL 07	**Trial-Number:** 502.491	**Study period (dates):** 24 JAN 06 – 30 JAN 07	

Title of study:	An open-label follow-up trial of the efficacy and safety of chronic administration of the fixed dose combination of telmisartan 80 mg + hydrochlorothiazide 25 mg tablets alone or in combination with other antihypertensive medications in patients with hypertension
Investigator:	[redacted]
Study centres:	Multi-centre study; 100 centres in 16 countries
Publication (reference):	Data from this study have not yet been published.
Clinical phase:	III
Objectives:	The primary objective was to assess the efficacy and safety of the fixed-dose combination (FDC) of telmisartan 80 mg and hydrochlorothiazide 25 mg (T80/H25), alone or in addition to other antihypertensive therapies, during open-label, long-term treatment. Efficacy endpoints included the proportion of patients achieving diastolic blood pressure (DBP) control, trough seated DBP and systolic blood pressure (SBP), proportions of patients with DBP response and SBP response and the proportions of patients with optimal, normal, high-normal and high blood pressure (BP). Safety was monitored by the assessment of physical examinations, laboratory parameters, 12-lead electrocardiogram (ECG) and reported adverse events (AEs).
Methodology:	Open-label treatment with T80/H25, no control group. BP was measured 24 hours post-dose at each visit; measurements taken 20-30 hours post-dose were considered as trough values.
No. of subjects:	
planned:	entered: 700
actual:	enrolled: 639 entered: 639 T80/H25: entered: 639 treated: 639 analysed (for primary endpoint): 633

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Diagnosis and main criteria for inclusion:	Male or female adult patients with previously treated essential hypertension who had completed the preceding trial 502.480 [U07-1110] within 14 days prior to entering the current trial. In trial 502.480, patients that had failed to respond adequately to 6 weeks of open-label therapy with the FDC of telmisartan 80 mg plus hydrochlorothiazide 12.5 mg (T80/H12.5) were randomised to an 8-week double-blind, parallel-group comparison of T80/H12.5 and T80/H25. Failure to respond adequately was defined as a trough seated DBP ≥90 mmHg.
Test product:	Telmisartan/hydrochlorothiazide (80 mg/25 mg) FDC
dose:	1 tablet (80 mg/25 mg) once daily
mode of admin.:	oral
batch no.:	505 982
Duration of treatment:	24 weeks
Reference therapy:	None
dose:	
mode of admin.:	
batch no.:	
Criteria for evaluation:	
Efficacy:	The primary endpoint was the proportion of patients achieving DBP control. Secondary endpoints were trough seated DBP and SBP, DBP response, SBP response, the proportions of patients with optimal, normal, high-normal and high BP, and the effect of additional antihypertensive therapy on BP.
Safety:	Laboratory assessments, 12-lead ECG and physical examinations, reported AEs.
Statistical methods:	Descriptive statistics
SUMMARY – CONCLUSIONS:	
	The results of an interim analysis (introduced by Amendment 2) of data from 432 patients are available in a separate clinical trial report [U07-1143-01].
Efficacy results:	Of the 639 patients, 94.8% completed the study; 5.2% discontinued prematurely, mostly due to AEs (3.1%). The population consisted mostly of white patients (88.6%). The proportion of males was 57.1%; the mean age was 57.0 years. The mean duration of hypertension was 7.5 years. Mean trough seated BP at the end of the preceding study was 140.9/89.0 mmHg. During treatment, 111 patients

Efficacy results: (continued)

(17.4% of the patients in the treated set) took additional antihypertensive medications, with calcium antagonists (11.0%) and beta blocking agents (5.9%) being most frequent.

While 52.4% of the patients in the full analysis set (FAS) had had DBP control (DBP <90 mmHg) at the end of the preceding study, this proportion increased to 71.4% at the end of this trial. The randomised treatment (i.e. T80/H12.5 or T80/H25) patients had received before entering this trial did not impact on the DBP control rates at the end of treatment. The results for the primary endpoint were similar in the per protocol set.

The results of the analyses of the secondary endpoints were consistent with that of the primary endpoint; all demonstrated additional BP-lowering during this study. Trough seated BP was reduced in the course of this trial from 141.0/89.0 mmHg to 136.4/85.5 mmHg. The BP reduction achieved in this trial was therefore −4.6/−3.6 mmHg. Approximately 80% of this reduction was seen after only one month of treatment (−3.7/−2.8 mmHg). The total BP reduction from baseline of trial 502.480 to end of this trial was −11.4/−9.7 mmHg. In the patients who did not receive additional antihypertensives, the total BP reduction was −11.5/−9.9 mmHg.

The proportion of patients with trough seated DBP response (DBP <90 mmHg or a reduction from baseline of the preceding study of ≥10 mmHg) increased from 55.8% at the end of the preceding study to 74.3% at the end of the present study. Trough seated SBP 140/10 response rates (SBP <140 mmHg or a reduction from baseline of the preceding study of ≥10 mmHg) increased from 60.3% to 77.8%. For trough seated SBP 140/20 response (SBP <140 mmHg or a reduction from baseline of the preceding study of ≥20 mmHg), the proportions of responders were 51.8% at the end of the preceding study and 69.3% at the end of this study.

With regard to the trough seated BP categories, 34.3% of the patients had reached target BP (SBP <140 mmHg and DBP <90 mmHg) at the end of the preceding trial. This proportion increased to 54.5% at the end of the current trial.

For the patients who took other antihypertensives in addition to T80/H25 (17.5% of the FAS patients), the median time to starting the additional treatment was 32 days with a median duration of intake of 142 days. A large proportion (81.8%) of the patients taking additional antihypertensives did not have DBP control prior to starting the additional therapy; however, the majority of these patients (53.3%) achieved DBP control by the end of the study.

Safety results:

The mean exposure to T80/H25 was 172.4 days; 85.4% of the patients had an exposure of at least 24 weeks and 34.3% of at least 26 weeks.

In total, 280 patients (43.8%) experienced AEs during treatment with T80/H25. The most frequently affected system organ classes (incidence ≥5%) were infections and infestations (15.3%), musculoskeletal and connective tissue disorders (11.4%), nervous system disorders (6.1%), and gastrointestinal disorders (5.6%). On preferred term level, the most frequent AEs (incidence ≥2%) were back pain (3.0%), nasopharyngitis (2.5%), and arthralgia (2.0%). In this trial, the patients that had received T80/H12.5 in the preceding trial had a slightly higher reported incidence of adverse events (47.5%) than the patients previously treated with T80/H25 (40.2%). AEs led to study drug discontinuation in 3.0% of the patients. The investigators considered AEs to be drug-related in 4.5% of the patients. AEs of severe intensity were reported by 3.3% of the patients.

Serious adverse events (SAEs) occurred in 18 patients (2.8%), 3 of whom died (no. 840: completed suicide, no. 9617: road traffic accident, no. 9122: breast cancer). None of the SAEs was considered drug-related by the investigator. Other significant AEs (i.e. non-serious AEs that led to drug discontinuation or dose reduction) affected 13 patients (2.0%).

There were no laboratory abnormalities reported as SAEs. Three patients discontinued the trial because of a laboratory-related AE (thrombocytopenia, abnormal hepatic function, increased blood creatinine); the increase of blood creatinine was considered drug-related by the investigator. Potassium concentrations below 3.5 mmol/L (as low as 3.2 mmol/L) were reported in 8 patients (1.3%) after baseline. The frequencies of patients with possibly clinically significant abnormalities were below 8% for all parameters. The highest frequencies of abnormalities were observed for triglycerides (7.5% with an increase) and uric acid (5.6% with an increase). Uric-acid related AEs were reported in 6 patients (0.9%); in 3 of these 6 patients, uric acid values were of possible clinical significance. Blood samples were not required to be obtained in the fasting state during this trial. There were no clear differences in observed laboratory abnormalities or reported laboratory value-related AEs based on the double-blind therapy patients had received in the prior trial.

No safety concerns were apparent on review of the data from physical examinations, vital signs or ECGs.

Conclusions:	Six months of long-term, open-label treatment with the fixed-dose combination T80/H25, with and without concomitant use of other antihypertensive agents, resulted in an additional BP reduction in patients that had previously been treated with telmisartan/HCTZ. In the preceding trial, patients with trough seated DBP ≥90 mmHg after a 6-week treatment with T80/H12.5 had been treated for 8 weeks with either T80/H12.5 or T80/H25. At the end of the present study, 71.4% of the patients had achieved trough DBP control compared with 52.4% at the end of the preceding trial. The additional reduction of trough seated BP in this study was −3.6 mmHg for DBP and −4.6 mmHg for SBP, regardless of which treatment patients had previously received. The observed safety profile of the fixed-dose combination product was consistent with that known for both individual products. Open-label treatment with T80/H25 was safe and well tolerated.