Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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..

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® HCT			
Names of active ingredients: Telmisartan plus hydrochlorothiazide		**Page 1 of 5**	
Report date: 06 FEB 07	**Trial-Number:** 502.480	**Study period (dates):** 11 OCT 05 – 03 AUG 06	**Date of Revision**

Title of study:	A prospective randomised study to compare a fixed dose combination of telmisartan 80 mg plus hydrochlorothiazide 25 mg with a fixed dose combination of telmisartan 80 mg plus hydrochlorothiazide 12.5 mg in patients with uncontrolled hypertension who fail to respond adequately to treatment with a fixed dose combination of telmisartan 80 mg plus hydrochlorothiazide 12.5 mg
Investigator:	[redacted]
Study centres:	Multi-centre study, 113 centres in 16 countries
Publication:	Data from this study have not been published.
Clinical phase:	III
Objectives:	Primary: to show that a fixed-dose combination (FDC) of telmisartan 80 mg plus hydrochlorothiazide 25 mg (T80/H25) was superior to an FDC of telmisartan 80 mg plus hydrochlorothiazide 12.5 mg (T80/H12.5) in reducing trough seated diastolic blood pressure (DBP) in patients who failed to respond adequately to T80/H12.5. Secondary: (i) to show that T80/H25 was superior to T80/H12.5 in reducing trough seated systolic blood pressure (SBP) in patients who failed to respond adequately to T80/H12.5; (ii) to show that T80/H25 was superior to T80/H12.5 in improving other blood pressure (BP) endpoints including trough standing SBP and DBP, proportions of patients achieving DBP control, DBP response and SBP response and proportions of patients with optimal, normal, high-normal and high BP; (iii) to monitor safety through physical examinations, laboratory parameters, 12-lead electrocardiogram (ECG) and reported adverse events (AEs).
Methodology:	Filter design with an open-label run-in treatment period (T80/H12.5) of 6 weeks and a randomised double-blind, double-dummy, parallel-group (1:1) treatment period (T80/H12.5 or T80/H25) of 8 weeks including only patients who failed to respond adequately to run-in treatment (DBP ≥90 mmHg at 6 weeks). BP was measured 24 hours post-dose at each visit; measurements taken 20-30 hours post-dose were considered as trough values.

Name of company: Boehringer Ingelheim International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: MICARDIS® HCT			
Names of active ingredients: Telmisartan plus hydrochlorothiazide		**Page 2 of 5**	
Report date: 06 FEB 07	**Trial-Number:** 502.480	**Study period (dates):** 11 OCT 05 – 03 AUG 06	**Date of Revision**

No. of subjects:	
planned:	entered: 480
actual:	enrolled: 1042 (Of these, 971 were included in the run-in phase.) entered: 713 T80/H12.5: entered: 361 treated: 361 analysed (for primary endpoint): 347 T80/H25: entered: 352 treated: 352 analysed (for primary endpoint): 340
Diagnosis and main criteria for inclusion:	Male or female adult patients with hypertension taking between 1 and 3 anti-hypertensive medications at screening and whose BP was not adequately controlled on existing therapy (inadequate control defined as seated DBP ≥95 mmHg on 1 or seated DBP ≥90 mmHg on 2 or 3 antihypertensive therapies). Patients were only randomised if they failed to respond adequately to T80/H12.5 (failure defined as seated DBP ≥90 mmHg after 6 weeks of treatment with T80/H12.5).
Test product:	Telmisartan/hydrochlorothiazide (80 mg/25 mg) fixed-dose combination
dose:	1 tablet (80 mg/25 mg) once daily
mode of admin.:	oral
batch no.:	505 982 (80 mg/25 mg), 506 171 (matching placebo)
Duration of treatment:	8 weeks
Reference therapy:	Telmisartan/hydrochlorothiazide (80 mg/ 12.5 mg) fixed-dose combination
dose:	1 tablet (80 mg/12.5 mg) once daily
mode of admin.:	oral
batch no.:	505 248 (80 mg/12.5 mg), 503 802 (matching placebo)
Criteria for evaluation:	
Efficacy:	Primary endpoint: change from baseline in trough seated DBP. Secondary endpoints: change from baseline in trough seated SBP, trough standing SBP and DBP; proportions of patients achieving DBP control, DBP response and SBP response and proportions of patients with optimal, normal, high-normal and high BP.
Safety:	Laboratory assessments, 12-lead ECG and physical examinations, reported AEs.

Statistical methods:	Analysis of covariance with treatment and country as main effects and baseline as a covariate, Mantel-Haenszel test controlling for country, and a stratified (for country) Wilcoxon rank sum test.

SUMMARY – CONCLUSIONS:

Efficacy results:

Of the 713 randomised patients, 3.8% discontinued the study prematurely (T80/H12.5: 4.7%, T80/H25: 2.8%). The randomised population consisted of 88.6% white patients; the proportion of male patients was 56.9% and the mean age was 57.2 years. Mean trough seated BP at the end of the run-in treatment, i.e. baseline, was 147.5/94.9 mmHg (T80/H12.5) and 148.0/95.3 mmHg (T80/H25). The treatment groups were generally well matched for demographic and baseline parameters.

The primary analysis showed superiority of T80/H25 over T80/H12.5. Adjusted mean changes from baseline in trough seated DBP were -5.5 mmHg (T80/H12.5) and -7.1 mmHg (T80/H25). The treatment difference (95% CI) of -1.6 mmHg (-2.5 mmHg, -0.6 mmHg) was statistically significant (p=0.0012). The per protocol set analysis confirmed the results of the above analysis of the full analysis set.

All analyses of secondary endpoints supported the primary analysis. For trough seated SBP, adjusted mean changes from baseline were -7.1 mmHg (T80/H12.5) and -9.8 mmHg (T80/H25). The treatment difference was -2.7 mmHg (-4.2 mmHg, -1.2 mmHg) with a p-value of 0.0003. Results for trough standing DBP and SBP were comparable to those for seated BP.

Trough seated DBP control (DBP <90 mmHg) was achieved by 49.0% (T80/H12.5) and 55.9% (T80/H25) of the patients (p=0.0641). The proportions of patients with DBP response (trough seated DBP <90 mmHg or a reduction ≥10 mmHg) were 51.9% (T80/H12.5) and 59.7% (T80/H25), with p=0.0336 for the treatment difference. Trough seated SBP response (SBP <140 mmHg or a reduction ≥20 mmHg) was reached by 48.1% (T80/H12.5) and 57.6% (T80/H25) of the patients (p=0.0103).

By the end of the trial, 32.0% (T80/H12.5) and 39.4% (T80/H25) of the patients had reached target BP (<140/90 mmHg), i.e. had an optimal, normal, or high-normal trough seated BP; the majority of the patients (68.0% vs. 60.6%) had a high BP. The between group difference for the distributions of patients across the 4 BP categories had a p-value of 0.0852.

Safety results:

The mean exposure to run-in treatment (T80/H12.5) was 41.8 days. Mean exposure to randomised treatment was 56.0 days for T80/H12.5 and 56.5 days for T80/H25.

Safety results: (continued)

During the run-in phase, 22.6% of the patients experienced AEs. The most frequently affected system organ classes (incidence ≥2%) were infections and infestations (6.1%), nervous system disorders (3.9%), gastrointestinal disorders (3.8%), and musculoskeletal and connective tissue disorders (3.7%). On preferred term level, the most frequent AEs (incidence ≥1%) were headache (2.0%), dizziness (1.3%), and nasopharyngitis (1.0%). Overall, 8 patients (0.8%) had severe AEs. Drug-related AEs occurred in 5.3% of the patients. AEs that led to premature discontinuation of treatment occurred in 27 patients (2.8%). Serious adverse events (SAEs) occurred in 4 patients (0.4%); none were considered to be related to treatment. Other significant AEs (non-serious AEs which resulted in discontinuation or dose reduction) affected 26 patients (2.7%).

During the randomised phase, 29.6% (T80/H12.5) and 31.5% (T80/H25) of the patients had AEs. The most frequently affected system organ classes (overall incidence ≥3%) were infections and infestations (7.2% of the T80/H12.5 patients and 6.5% of the T80/H25 patients), musculoskeletal and connective tissue disorders (6.1% vs. 5.4%), gastrointestinal disorders (4.2% vs. 4.3%), and nervous system disorders (4.4% vs. 3.4%). On preferred term level, the most frequent AEs (overall incidence ≥1% or 8 patients) were back pain (1.9% vs. 2.0%), bronchitis (2.2% vs. 1.1%), headache (2.8% vs. 0.6%), palpitations (1.4% vs. 0.9%), and nasopharyngitis (0.6% vs. 1.7%). Severe AEs were reported by 1.4% (T80/H12.5) and 2.0% (T80/H25) of the patients. Drug-related AEs occurred in 5.0% (T80/H12.5) and 5.7% (T80/H25) of the patients. The frequencies of discontinuations due to AEs were 3.0% (T80/H12.5) and 1.7% (T80/H25). One patient (T80/H25) died because of a head injury after falling from a bicycle. SAEs occurred in 0.8% (T80/H12.5) and 1.4% (T80/H25) of the patients. Two SAEs were considered drug-related (T80/H12.5: atrioventricular block third degree, T80/H25: atrial flutter). Other significant AEs affected 2.8% (T80/H12.5) and 1.1% (T80/H25) of the patients.

No patient discontinued due to a treatment-emergent laboratory abnormality reported as an AE. No SAEs due to laboratory abnormalities were reported. Overall, the numbers of patients with possibly clinically significant abnormalities were low. The following changes of laboratory parameters were more prominent in the T80/H25 group than in the T80/H12.5 group: increases of uric acid, creatine kinase, and urea as well as decreases of haematocrit and haemoglobin.

Hypokalaemia (potassium level <3.5 mmol/L) occurred only in 2 patients on run-in or randomised treatment with T80/H12.5 and in one patient on T80/H25. There were no relevant differences between T80/H12.5 and T80/H25 with regard to physical examination data, including pulse rates and weight, nor for ECG data.

Name of company: Boehringer Ingelheim International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: MICARDIS® HCT			
Names of active ingredients: Telmisartan plus hydrochlorothiazide		**Page 5 of 5**	
Report date: 06 FEB 07	**Trial-Number:** 502.480	**Study period (dates):** 11 OCT 05 – 03 AUG 06	**Date of Revision**

Conclusions:	Treatment with T80/H25 in patients with hypertension not adequately controlled by T80/H12.5 led to an additional, clinically relevant BP reduction. T80/H25 was superior to T80/H12.5 in reducing trough seated DBP after 8 weeks of randomised treatment. All analyses of secondary efficacy endpoints such as trough seated SBP, standing BP, and BP control and response showed better results for the T80/H25 group than for the T80/H12.5 group. Both treatments were well tolerated.