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		**Tabulated Study Report**		
Name of finished product: Micardis PLUS				
Name of active ingredient: Telmisartan, Hydrochlorothiazide, BIBR 277 HCT		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 16 December 2004	**Number:** U04-3528-01	**Study period (dates):** 1 December 2003 to 15 February 2004		**Revision date:** 14 December 2005

Title of study:	Safety, tolerability and pharmacokinetics of single rising oral doses (40 mg Telmisartan / 12.5 mg HCTZ to 80 mg Telmisartan / 12.5 mg HCTZ) and multiple oral doses (80 mg Telmisartan / 12.5 mg HCTZ) of drug in healthy male volunteers
Investigator:	[redacted]
Study center(s):	[redacted] Japan
Publication (reference):	Not yet published
Clinical phase:	I
Objectives:	To investigate safety, tolerability and pharmacokinetics of Telmisartan + HCTZ (T40/H12.5 and T80/H12.5) To investigate safety, tolerability and pharmacokinetics of Telmisartan + HCTZ (T80/H12.5 x 7 days)
Methodology:	Open-label, Randomised, single and multiple doses
No. of subjects:	
planned:	entered: 20
actual:	enrolled: 26 Group 1: single rising oral doses (Telmisartan 40 mg / HCTZ 12.5 mg to Telmisartan 80 mg / HCTZ 12.5 mg) enrolled: 13 entered: 10 and analysed: 10 Group 2: multiple oral doses (Telmisartan 80 mg / HCTZ 12.5 mg) enrolled: 13 entered: 10 and analysed: 10
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥20 and ≤35 years, BMI range: ≥17.6 and ≤26.4 kg/m^2
Test product:	Telmisartan 40 mg or 80 mg tablets, HCTZ 12.5 mg tablets
dose:	Group 1: Single-dose Telmisartan 40 mg / HCTZ 12.5 mg, Telmisartan 80 mg / HCTZ 12.5 mg Group 2: Multiple-dose Telmisartan 80 mg / HCTZ 12.5 mg x 7 days
mode of admin.:	oral

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batch no.:	Telmisartan 40 / 80 : 106505 / 206065 Hydrochlorotiazide : F5074
Duration of treatment:	Group 1: single dose x 2 periods Group 2: 7 days
Reference therapy:	N / A
dose:	
mode of admin.:	
batch no.:	
Criteria for evaluation:	
Pharmacokinetics:	Group 1: Single-dose Telmisartan: C_{max}, t_{max}, AUC_{t1-t2}, $AUC_{0-\infty}$, AUC_{0-tz}, λ_Z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F HCTZ: C_{max}, t_{max}, AUC_{t1-t2}, $AUC_{0-\infty}$, AUC_{0-tz}, λ_Z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$ Group 2: Multiple-dose Telmisartan: $C_{max,1}$, $t_{max,1}$, $AUC\tau_{,1,}$ $C_{max,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$ $C_{min,ss}$, C_{avg}, $MRT_{po,ss}$, $CL/F_{,ss}$, $Vz/F_{,ss}$, R_A HCTZ: $C_{max,1}$, $t_{max,1}$, $AUC\tau_{,1}$, $Ae_{t1-t2,1}$, $fe_{t1-t2,1}$, $CL_{R,1,}$ $C_{max,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$ $C_{min,ss}$, C_{avg}, $MRT_{po,ss}$, $CL/F_{,ss}$, $Vz/F_{,ss}$, R_A, $Ae_{t1-t2,ss}$, $fe_{t1-t2,ss}$, $CL_{R,ss}$
Safety:	Physical examination, vital signs (BP, PR, body temperature), 12-lead resting ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Descriptive statistics for safety assessments and PK parameters will be calculated. The occurrence of adverse events will comprise various frequency tabulations. Laboratory values will be listed, tabulated and refer to the normal ranges. Safety will be assessed by the change (from screening and/or baseline) of physical examination, vital signs (BP, PR, body temperature), and 12-lead ECG. Global assessment of tolerability is done by the investigator.

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SUMMARY – CONCLUSIONS:

Pharmacokinetics results: Following single administration of T40/H12.5 and T80/H12.5, telmisartan plasma concentrations increased more than proportionally to the dose and HCTZ plasma concentrations were similar in the two dose groups. The average cumulative urinary excretion of HCTZ was about 80–90 % of the dose.

After multiple administration of T80/H12.5 for 7 days, ratios of accumulation for telmisartan and HCTZ were in the range of 1.34-1.50 and 1.10-1.11, respectively. The values of t_{max} and elimination half-life on day 7 were similar to the single administration data. HCTZ was mainly excreted into urine.

From the result of preliminary comparison of pharmacokinetic profiles after single administration of T40/H12.5 and T80/H12.5 in Japanese with those in Caucasians, plasma concentrations of telmisartan in Japanese were higher than those in Caucasians. After normalization of pharmacokinetic parameters by body weight, the difference became smaller but those in Japanese were still higher. Pharmacokinetic profiles of HCTZ in Japanese and Caucasians were considered to be essentially similar with or without weight normalization.

Safety results: There were several adverse events whose relationships with trial drug were not denied during the trial. Clinical abnormalities were not reported in subjective and objective symptoms. And there were no clinical abnormalities in physiologic and medical examinations.

Conclusions: Multiple doses of T80/H12.5 mg once-daily for 7 days have not shown any issue in term of safety and tolerability.