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: BIBR 277 HCT, telmisartan + hydrochlorothiazide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 24 August 2005	**Number:** U05-3267	**Study period (dates):** 6 February 2005 – 28 February 2005		

Title of study:	Bioequivalence of 80 mg telmisartan/12.5 mg HCTZ of fixed dose combination compared to its monocomponents in healthy male volunteers (an open-label, randomised, single-dose, two-way crossover study)
Investigator:	[redacted]
Study centre:	[redacted] Japan
Publication (reference):	Data of this study has not been published.
Clinical phase:	I
Objectives:	To establish the bioequivalence of 80 mg telmisartan/12.5 mg HCTZ fixed dose combination vs. its monocomponents
Methodology:	Open-label, randomised, single-dose, two-way crossover design
No. of subjects:	
planned:	36
actual:	enrolled: 36 (all subjects received both 80 mg telmisartan/12.5 mg HCTZ fixed dose combination and its monocomponents) fixed dose combination of 80 mg telmisartan/12.5 mg HCTZ followed by its monocomponents: entered: 18 treated: 18 analysed (for pharmacokinetics and safety): 18 monocomponents of 80 mg telmisartan and 12.5 mg HCTZ followed by the fixed dose combination: entered: 18 treated: 18 analysed (for pharmacokinetics and safety): 18
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age: ≥20 and ≤35 years, BMI range: ≥17.6 and ≤25.0 kg/m^2
Test product:	Telmisartan and HCTZ, fixed dose combination tablet
dose:	80 mg telmisartan/12.5 mg HCTZ
mode of admin.:	Oral administration after an overnight fast for at least 10 hours, with 150 mL water
batch no.:	B04115

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Micardis® Plus		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BIBR 277 HCT, telmisartan + hydrochlorothiazide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 24 August 2005	**Number:** U05-3267	**Study period (dates):** 6 February 2005 – 28 February 2005		

Duration of treatment:	1 day for each treatment
Reference therapy:	Telmisartan tablet and HCTZ tablet
dose:	80 mg telmisartan and 12.5 mg HCTZ
mode of admin.:	Oral administration after an overnight fast for at least 10 hours, with 150 mL water
batch no.:	Telmisartan: 401508, HCTZ: B03026
Criteria for evaluation:	
Pharmacokinetics:	Primary endpoints: AUC_{0-tz}, and C_{max} Secondary endpoints: $AUC_{0-\infty}$, t_{max}, λ_z, $t_{1/2}$, MRT_{po}
Safety:	Physical examination, vital signs (blood pressure, pulse rate), ECG, laboratory tests, adverse events
Statistical methods:	Pharmacokinetic parameters of telmisartan and HCTZ were evaluated separately. Two-sided 90% confidence intervals (CIs) for the intra-subject ratio (as estimated by the geometric mean of the ratio) of each of AUC_{0-tz} and C_{max} was calculated to determine whether the CIs were contained in the acceptance range of 80-125% for bioequivalence. Additionally, the corresponding point estimators (geometric means) for the median intra-subject ratios were provided. The statistical model was an analysis of variance (ANOVA) on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters was calculated. Frequencies were tabulated for all categorical parameters.
SUMMARY – CONCLUSIONS:	
Pharmacokinetic results:	<u>Assessment of bioequivalence (Telmisartan)</u> The ratios of the adjusted mean values of C_{max} and AUC_{0-tz} of fixed dose combination to those of monocomponents were 1.143 and 1.084, respectively. The degrees of intra-individual variability of C_{max} and AUC_{0-tz} calculated from the mean square errors were 45.1 % and 15.6 %, respectively. The 90% CIs were from 96.3 to 135.7% for C_{max} and from 101.9% to 115.4% for AUC_{0-tz}. The 90% CI for AUC_{0-tz} of telmisartan fell in the acceptance range (80-125%), while the 90% CI for C_{max} of telmisartan did not fall in the acceptance range (80-125%). Therefore, bioequivalence of telmisartan was not proven in this trial.

Name of company: Boehringer Ingelheim		**Tabulated Study Report** **SUPPLEMENTARY SHEET**		
Name of finished product: Micardis® Plus				
Name of active ingredient: BIBR 277 HCT, telmisartan + hydrochlorothiazide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 24 August 2005	**Number:** U05-3267	**Study period (dates):** 6 February 2005 – 28 February 2005		

	Assessment of bioequivalence (HCTZ) The ratios of the adjusted mean values of C_{max} and AUC_{0-tz} of fixed dose combination to those of monocomponents were 0.929 and 0.974, respectively. The degrees of intra-individual variability of C_{max} and AUC_{0-tz} calculated from the mean square errors were 15.3% and 10.1%, respectively. The 90% CIs were from 87.5% to 98.7% for C_{max} and from 93.6% to 101.4% for AUC_{0-tz}. Although the upper limit of the 90% CI for C_{max} was slightly lower than unity, the 90% CI for C_{max} was within the acceptance range (80-125%). Therefore, bioequivalence of HCTZ was proven in this trial.
Safety results:	There was 1 adverse event: dizziness postural in 1 subject. The event was related to the study drug. This adverse event was mild and the subject recovered without treatment. No serious adverse event occurred. We concluded that telmisartan 80 mg and HCTZ 12.5 mg, which were concomitantly administered to healthy subjects both in fixed dose combination and in monocomponents, were well tolerated.
Conclusions:	The results of analysis for telmisartan did not meet the bioequivalence criteria. Although the 90% CI for AUC_{0-tz} of telmisartan fell in the bioequivalence range (80-125%), the 90% CI for C_{max} of telmisartan did not. The results of analysis for HCTZ met the bioequivalence criteria, so the fixed dose combination and monocomponents were proven to be bioequivalent for HCTZ. Thus fixed dose combination and monocomponents of telmisartan 80 mg and HCTZ 12.5 mg were proven to be bioequivalent for HCTZ, but not for telmisartan in this trial.