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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: CoMicardis/Micardis Plus				
Name of active ingredient: Telmisartan plus hydrochlorothiazide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** xxx to xxxx		**Addendum No.:**
Report date: 20 October, 2000	**Number:** U00-3262	**Study period (years):** 05 January 2000 to 15 May 2000		

Title of study:	An Eight Week Randomized, Double-Blind Study Comparing a Fixed Dose Combination of Telmisartan 40 mg Plus Hydrochlorothiazide 12.5 mg to Telmisartan 40 mg in Patients Who Fail to Respond Adequately to Treatment With Telmisartan 40 mg.
Investigator:	[redacted]
Study center(s):	12 centres
Publication (reference):	
Clinical phase:	IIIb
Objectives:	*Primary:* to demonstrate that a fixed dose combination of T40 mg plus HCTZ 12.5 mg is superior to T40 mg alone in lowering seated trough diastolic blood pressure after eight weeks in patients who fail to respond adequately to telmisartan monotherapy. *Secondary:* i) to demonstrate that a fixed dose combination of T40 mg plus HCTZ 12.5 mg is superior to T40 mg alone in lowering seated trough systolic blood pressure after eight weeks in patients who fail to respond adequately to telmisartan monotherapy. ii) to monitor safety through phys. exams., lab. parameters, 12-lead ECG and adverse events.
Methodology:	All patients entered a three to 30 day (to allow for adequate washout of prior anti-hypertensive medication, if required) screening phase prior to starting the four-week open-label T40 mg period. At the end of four weeks only patients who failed to respond adequately to T40 mg (DBP ≥ 90 mm Hg) were randomized, double-blind, to receive either T40 mg alone or the fixed dose combination of T40 mg plus HCTZ 12.5 mg for eight weeks. Seated BP was taken 24 hours post-dose at each visit. Labs, ECG, and physical examination were done at screening, at reference baseline (Visit 3) and at the final visit.
No. of subjects entered:	
total:	327
each treatment:	Telm 40: 167; FDC 40/12.5: 160
Diagnosis and main criteria for inclusion:	Male or female patients with a history of mild-to-moderate hypertension taking no more than three anti-hypertensive medications at screening and who failed to respond adequately to telmisartan monotherapy.

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Test product:	Fixed dose combination of telmisartan plus HCTZ; matching placebo
dose:	40 mg/12.5 mg once daily
mode of admin.:	tablet, p.o.
batch no.:	active: PD – 1947; placebo: PD - 1948
Duration of treatment:	
Reference therapy:	MICARDIS® (telmisartan, BIBR 277 SE) with matching placebo
dose:	40 mg, once daily
mode of admin.:	tablet, p.o.
batch no.:	active: PD – 1949; placebo: PD - 1950
Criteria for evaluation:	
Efficacy:	Seated DBP and SBP at trough
Safety:	Reports of AEs, and laboratory assessments, physical exams, and ECG at screening, at reference baseline (Visit 3) and at end of double-blind phase
Statistical methods:	Analysis of covariance; Mantel-Haenszel test
SUMMARY - CONCLUSIONS:	
Efficacy results:	Treatment with FDC 40/12.5 lowered DBP by an additional 3.5 mm Hg and SBP by 7.4 mm Hg compared to Telm 40 in this group of non-responders to Telm 40 monotherapy. Both were highly statistically significant (p-value < 0.01). Most of the additional effect was seen at four weeks of treatment. Changes in DBP for Telm 40 at week 4 were –4.8 mm Hg and at week 8, -4.3 mm Hg. Changes in DBP for FDC 40/12.5 at week 4 were –6.1 mm Hg and at week 8, -7.4 mm Hg. Patients in the FDC 40/12.5 arm had a normalized BP response rate (SBP <140 mm Hg and DBP < 90 mm Hg) of 51.6% compared to 23.5% for patients in the Telm 40 arm. The DBP response rate (DBP < 90 mm Hg) for FDC 40/12.5 was 64.8% compared to 40.1% for Telm 40. The SBP response rate (reduction in SBP ≥ 10 mm Hg from start of active treatment) for FDC 40/12.5 was 63.5% compared to 42.6% for Telm 40. No statistical differences were found with regard to age or gender between the two treatment groups.

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Safety results:

Overall, both treatments were very well tolerated. The frequency of adverse events reported in this trial were similar to those found in previous trials in which HCTZ was used in conjunction with telmisartan (U97-3070, U99-3137, U00-3112). Fifty-eight (34.7%) patients on Telm 40 compared to 68 (42.5%) patients on FDC 40/12.5 reported an adverse event. Although dizziness was reported slightly more often by FDC 40/12.5 patients compared to Telm 40 patients, the difference between incidence rates was not significant (5.6% versus 1.8%; p=0.081 by Fisher's exact test). For all other reported events there were no statistically or clinically relevant differences between treatment groups. Furthermore, most of the adverse events in both groups were mild (about 66% for each group) and transient in nature and most (Telm40, about 78%; FDC 40/12.5, about 70%) were classed as non-drug related by the Investigator.

One patient on Telm 40 reported a serious adverse event (intermittent chest pain of mild intensity) during the double-blind treatment period. This event was not considered drug-related and the patient was not withdrawn due to the event; in fact, the patient only admitted to the chest pain after the final visit had occurred. Only seven patients (three on Telm 40 and four on FDC 40/12.5) were discontinued due to adverse events. All but one of these events was deemed drug related by the Investigator.

There were few new or worsening physical or ECG findings in either treatment group. There were also no meaningful clinically relevant changes in any of the laboratory parameters measured. In particular, in the FDC 40/12.5 group, there were no clinically relevant changes in electrolytes (particularly potassium) or metabolic parameters (e.g., uric acid, glucose, or lipids) that are known to be affected by the use of HCTZ.

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Conclusions:

In conclusion, the trial results indicate that treatment with FDC 40/12.5 is clinically and statistically superior to treatment with Telm 40 monotherapy in patients shown to be non-responders to Telm 40 monotherapy.

These results are consistent with those reported in an earlier factorial trial (U97-3070) that evaluated the anti-hypertensive efficacy of two specific telmisartan/HCTZ combinations relative to their individual components in patients with mild-to-moderate hypertension. In that study concomitant treatment with Telm 40 and HCTZ 12.5 reduced trough supine DBP by a further 1.9 mm Hg and SBP by 6.6 mm Hg compared to Telm 40 alone. The recently reported study comparing FDC 80/12.5 to Telm 80 (U00-3112) also showed much the same result in that trough supine DBP was reduced by a further 3.1 mm Hg and SBP by 5.7 mm Hg.

Another published study (R00-0226) with similar results compared the combination of valsartan and HCTZ to valsartan monotherapy in patients who failed to respond adequately (DBP $\geq$ 95 mm Hg) to valsartan monotherapy. In this study, treatment with the combination of valsartan 80 mg plus HCTZ 12.5 lowered DBP by an additional 3.2 mm Hg and SBP by 5.9 mm Hg compared to valsartan 80 mg monotherapy.

The observed BP response rates for this trial may be lower than that of other hypertensive trials due to the design of this trial. The filter design of this trial selected only those patients that were not controlled with Telm 40 monotherapy at the end of the four-week qualification period. Thus, the response rates observed for this sub-population of hypertensive patients would be expected to be lower than the response rate seen for the general hypertensive population. Additionally, the SBP response rate might be lower than other trials since this response rate is calculated using the pseudo-baseline measured at Visit 2 (where patients had as few as three days washout from previous anti-hypertensive medication.

There were no clinically relevant differences in the safety profile between FDC 40/12.5 and Telm 40 monotherapy.