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: MICARDIS®				
Name of active ingredient: Telmisartan (BIBR 277 SE)		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** xxx to xxxx		**Addendum No.:**
Report date: 05April2000	**Number:**	**Study period (years):** 0.6		

Title of study:	An Eight Week Randomized, Double-Blind Study Comparing a Fixed Dose Combination of Telmisartan 80 mg Plus Hydrochlorothiazide 12.5 mg to Telmisartan 80 mg in Patients Who Fail to Respond Adequately to Treatment With Telmisartan 80 mg.
Investigator:	[redacted]
Study centre(s):	15
Publication (reference):	
Clinical phase:	IIIb
Objectives:	*Primary:* to demonstrate that a fixed dose combination of telmisartan 80 mg plus hydrochlorothiazide (HCTZ) 12.5 mg (FDC 80/12.5) is superior to telmisartan 80 mg (Telm 80) alone in patients who failed to respond adequately to Telm 80 monotherapy in lowering seated trough diastolic blood pressure (DBP) after eight weeks of treatment. *Secondary:* i) to demonstrate that FDC 80/12.5 is superior to Telm 80 alone in patients who failed to respond adequately to Telm 80 monotherapy in lowering seated trough systolic blood pressure (SBP) after eight weeks of treatment. ii) To demonstrate that FDC 80/12.5 is superior to Telm 80 alone in patients who failed to respond adequately to telmisartan monotherapy in lowering standing trough DBP and SBP after eight weeks of treatment. iii) To monitor safety through physical exams laboratory parameters, ECG and adverse events (AEs).
Methodology:	All patients entered a one-week screening phase prior to starting the four-week open-label telmisartan 40 mg (Telm 40) period. At end of four weeks only patients who failed to respond adequately to Telm 40 (DBP ≥ 90 mm Hg) were titrated to Telm 80. At the end of four weeks, only patients who failed to respond adequately to Telm 80 (DBP ≥ 90 mm Hg) were randomized to receive either Telm 80 alone or FDC 80/12.5 for eight weeks. Seated BP was to be taken 24 hours post-dose at each visit. Labs, ECG, and physical exam.were done at screening, at reference baseline (Visit 4) and at the final visit.
No. of subjects entered:	
total:	491
each treatment:	Telm 80: 245; FDC 80/12.5: 246
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:	80 mg/12.5 mg once daily
mode of admin.:	tablet, p.o.
batch no.:	active: PD – 1883; placebo: PD - 1882
Duration of treatment:	8 weeks
Reference therapy:	MICARDIS® (telmisartan, BIBR 277 SE) with matching placebo
dose:	80 mg, once daily
mode of admin.:	tablet, p.o.
batch no.:	active: PD – 1881; placebo: PD - 1880
Criteria for evaluation:	
Efficacy:	Seated and standing DBP and SBP at trough
Safety:	Reports of AEs, and laboratory assessments, physical exams, and ECG at screening, at reference baseline (Visit 4) and at end of double-blind phase
Statistical methods:	Analysis of covariance; Mantel-Haenszel test.

SUMMARY - CONCLUSIONS:

Efficacy results:

Treatment with FDC 80/12.5 lowered DBP by an additional 3.1 mm Hg and SBP by 5.7 mm Hg compared to Telm 80 in this group of non-responders to Telm 80 monotherapy. Both were highly statistically significant (p-value < 0.01). Similar results were seen with standing blood pressure (BP). Most of the additional effect was seen at four weeks of treatment. Patients in the FDC 80/12.5 arm had a significantly greater BP response rate (SBP <140 mm Hg and DBP < 90 mm Hg) of 41.5% compared to 26.1% for patients in the Telm 80 arm ($p<0.05$).

No statistical differences were found with regard to gender between the two treatment groups. Although there were no age differences between treatment groups for DBP response, a trend was observed for a greater SBP response in the elderly. This in part could be due to the fact that the elderly generally respond well to treatment with hydrochlorothiazide (HCTZ).

These results are similar to 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 80 and HCTZ 12.5 mg reduced trough supine DBP by a further 3.4 mm Hg and SBP by 8.5 mm Hg compared to Telm 80 alone. However, there was a difference in the BP response rates between the two studies. The BP response rate in the factorial trial was 56.0% compared to 41.5% in this trial. This difference is most likely

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Efficacy results (cont.):	due to the difference in study design in that the patients in this study were a selected group of non-responders to Telm 80 monotherapy. Another published study with similar results compared the combination of valsartan and HCTZ to valsartan (V) monotherapy in patients who failed to respond adequately (DBP ≥ 95 mm Hg) to V monotherapy. In this study, treatment with the combination of V 80 mg plus HCTZ 12.5 mg lowered DBP by an additional 3.2 mm Hg and SBP by 5.9 mm Hg compared to V 80 mg monotherapy.
Safety results:	Both Telm 80and FDC 80/12.5 were well tolerated during the eight-week double-blind treatment period. Most of the AEs in both groups were mild and transient in nature. The frequency and intensity of AEs reported in this trial were similar to those found in previous trials in which HCTZ was added to telmisartan monotherapy (U99-3137). The frequency of AEs during double-blind treatment was comparable between the two treatment groups except for diarrhea and edema. Significantly more patients (10, 4.1%) on the FDC 80/12.5 compared to Telm 80 (none) reported diarrhea. However, this is probably not a clinically relevant finding as only two patients had an onset of diarrhea within a reasonable timeframe (three days) of starting FDC 80/12.5. Furthermore, one of these patients had underlying coeliac disease and had experienced enteritis during treatment with open-label Telm 40. And, for at least three of the patients, diarrhea could be attributed to another cause. Edema was reported in more patients (9, 3.7%) on Telm 80 compared to FDC 80/12.5 (2, 0.8%). This difference may have been due to the added diuretic effect of the HCTZ component of FDC 80/12.5. Only three patients (two on Telm 80and one on FDC 80/12.5) reported serious AEs during the double-blind treatment period. None of the events were considered drug-related and none of the patients were withdrawn due to the event. Six patients (four on Telm 80and two on FDC 80/12.5) were discontinued due to AEs with one patient from each group being withdrawn due to a drug-related AE. 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 80/12.5 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.
Conclusions:	In conclusion, the trial results indicate that treatment with FDC 80/12.5 is clinically and statistically superior to treatment with Telm 80 monotherapy in patients that were previously shown to be non-responders to Telm 80 monotherapy. Furthermore, there were no clinically relevant differences in the safety profile between FDC 80/12.5 and Telm 80 monotherapy.