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:** to		**Addendum No.:**
Report date: 23 March 2001	**Number:** 502.254	**Study period (years):** 18 Oct 1999 – 07 Aug 2000		

Title of study:	A randomised, double-blind, placebo-controlled, 6 week parallel-group trial on the efficacy and safety of the angiotensin II receptor antagonist Micardis® (telmisartan 20 mg, 40 mg or 80 mg, p.o. once daily) or hydrochlorothiazide 12.5 mg p.o. once daily in the management of patients with isolated systolic hypertension (ISH). **(ARAMIS - study = Angiotensin II Receptor Antagonist Micardis in Isolated Systolic Hypertension)**
Investigator:	Coordinating investigator: [redacted]
Study centre(s):	100 centres in 17 countries
Publication (reference):	none
Clinical phase:	IIIb/IV
Objectives:	The primary objective of this trial was to identify doses of Micardis® (telmisartan) which, administered once daily, are more effective than placebo and not inferior to HCTZ in lowering systolic blood pressure (SBP) in patients with isolated systolic hypertension (ISH), and to assess the dose response relationship of the antihypertensive effect of telmisartan over the dose range of 20 to 80 mg. The secondary objectives were to establish: the percentage of patients achieving a target fall in SBP; the change from baseline in through seated DBP after 6 weeks of treatment; safety and tolerability of Micardis® and HCTZ in patients with ISH as measured by changes in physical examinations, heart rate, laboratory parameters and/or 12-lead ECG, as well as the incidence and severity of adverse events.
Methodology:	After a 2 - 4 week single-blind placebo run-in period, patients were randomised to one of five double-blind treatments (placebo, telmisartan 20 mg, telmisartan 40 mg, telmisartan 80 mg, or HCTZ 12.5 mg). Double-blind trial drug was taken once-daily in the morning for a period of 6 weeks. Seated (24 hours post-dose) cuff blood pressure and heart rate was measured at each visit.
No. of subjects entered:	
total:	1039 randomised patients
each treatment:	211 patients treated with placebo; 206 patients treated with Telmisartan 20 mg; 210 patients treated with Telmisartan 40 mg; 207 patients treated with Telmisartan 80 mg; 205 patients treated with HCTZ 12.5 mg

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Diagnosis and main criteria for inclusion:	Patients aged 35 or more, but less than 85, with a systolic blood pressure of ≥ 150 mmHg and < 180 mmHg and a diastolic blood pressure of < 90 mmHg at the end of the run-in period (baseline visit 2). Patients receiving antihypertensive medication before start of the run-in period were included if antihypertensive medication could be stopped without risk to the patient's health.	
Test product:	Telmisartan	
dose:	20, 40 , 80 mg	
mode of admin.:	Tablet, oral	
batch no.:	902304, 9990018, 901855	
Duration of treatment:	6 weeks	
Reference therapy:	Placebo	
dose:	NA	
mode of admin.:	Tablet, oral	
batch no.:	902260, 902165, 9980238, F4835	
Reference therapy	Hydrochlorothiazide (HCTZ)	
Dose:	12.5 mg	
mode of admin.:	Tablet, oral	
Batch no.:	F4836	
Criteria for evaluation:		
Efficacy:	*Primary:*	Change from baseline in seated systolic blood pressure at trough (24 hours post-dose) after 6 weeks of treatment.
	Secondary:	Percentage of patients achieving a target fall in SBP after 6 weeks of treatment, change from baseline in seated diastolic blood pressure (DBP) after 6 weeks of treatment.

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Safety:	Safety and tolerability of telmisartan in terms of: i) Changes in physical examinations, heart rate, laboratory parameters, and/or 12-lead ECG, and ii) Incidence and severity of adverse events.
Statistical methods:	An ANCOVA model with baseline as covariate, country and treatment as main effects and the interaction treatment and country was used for the primary efficacy endpoint (24-hour trough cuff SBP) as well for the secondary endpoint DBP. The response rate to target fall in SBP was analysed for treatment differences by Fisher's Exact Test.

SUMMARY - CONCLUSIONS:

Efficacy results:

All doses of telmisartan (20, 40 and 80 mg) were superior to placebo in reducing SBP in patients with isolated systolic hypertension and at least as effective compared to the active reference HCTZ 12.5 mg. The mean change from baseline in SBP at through after 6 weeks of treatment was –15.6 (N=204) in the 20 mg, –17.9 (N=209) in the 40 mg, –16.9 (N=205) in the 80 mg telmisartan group, compared to –11.4 (N=208) in the placebo and –15.7 (N=204) in the HCTZ group. Adjusted mean differences to placebo were -4.23, -6.52 and - 5.58 for the telmisartan 20, 40 and 80 mg doses and -4.32 for HCTZ 12.5 mg.
95% CI for adjusted mean differences from placebo were for telmisartan 20 mg (–7.1, –1.3), telmisartan 40 mg (–9.4, –3.7), telmisartan 80 mg (–8.5, –2.7) and HCTZ (–7.2, –1.4). The efficacy of the telmisartan 20 mg dose gained 2/3 of the effect of the higher telmisartan doses (40 and 80 mg), but no statistically significant differences were found between different telmisartan doses.
The efficacy of HCTZ 12.5 mg was comparable to 20 mg of telmisartan.
Consistent results were found in the analysis of the target response (secondary efficacy endpoint). The percentage of patients who reached the target goal (SBP ≤140 mmHg or reduction by ≥20 mmHg) was highest in the telmisartan 80 mg group (53.7%), followed by 51.7% in the 40 mg group and of 46.6% in the 20 mg group, confirming the superiority of all telmisartan doses versus placebo (27.4%) as well as the non-inferiority of telmisartan versus HCTZ (42.6%).

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Safety results:

This 6 week randomised study confirmed the favourable safety profile of telmisartan in a dose range of 20 to 80 mg. The adverse events profile of all telmisartan treatment regimens (20, 40 and 80 mg) were comparable to placebo and also comparable to the active control HCTZ 12.5 mg.
The incidence rate of adverse events (19.9%, 17.6% and 20.3% in the 20, 40 and 80 mg telmisartan groups, compared to 20.9% in placebo and of 22.0% in HCTZ treated patients) was low, comparable between all treatment groups and without any detectable dose-related increase in the telmisartan treatment groups.
The incidence of serious adverse events was very low and none of the SAEs was judged to be "drug related" by the investigator or the clinical monitor.
The laboratory values of all investigated parameters did not indicate any relevant changes between baseline and end of study in either treatment group with exception of slightly, not clinically significant increased uric acid values in the group of HCTZ 12.5 mg treated patients.

Conclusions:

The study achieved the primary objective to demonstrate superiority of all doses of telmisartan (20, 40 and 80 mg) compared to placebo in reducing SBP in patients with isolated systolic hypertension as well as non-inferiority compared to the active comparator HCTZ 12.5 mg.
The efficacy of the telmisartan 20 mg dose gained only 2/3 of the effect of the higher telmisartan doses (40 and 80 mg), but no statistically significant differences were found between different telmisartan doses.
The efficacy of HCTZ 12.5 mg was comparable to 20 mg of telmisartan.
The results were confirmed by analysis of the target response as secondary endpoints of efficacy.
The safety profile of all telmisartan doses was comparable to placebo, without any detectable dose-related increase in the telmisartan treatment groups and also comparable to the active control HCTZ 12.5 mg.