Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: MICARDIS PLUS®			
Name of active ingredient: telmisartan and hydrochlorothiazide		**Page: 1 of 8**	
Report date: 2 Mar 2007	**Trial-Number:** 502.472	**Study period (years):** 28 Apr 2005- 15 Sep 15 2006	

Title of study:	An Eight Week Randomized, Double-Blind, Double-Dummy Study Comparing a Fixed Dose Combination of Telmisartan 80mg Plus Hydrochlothiazide 12.5mg to Telmisartan 80mg in Patients Who Fail to Respond Adequately to Treatment With Telmisartan 80mg.
Investigator:	[redacted]
Study center(s):	9 clinical trial centers in China. [redacted]
Publication (reference):	No
Clinical phase:	IIIb
Objectives:	*Primary:* To demonstrate that a fixed dose combination of telmisartan 80 mg plus HCTZ 12.5 mg is superior to telmisartan 80 mg alone in patients, who fail to respond adequately to telmisartan 80 mg monotherapy, in lowering seated trough diastolic blood pressure after eight weeks of treatment. *Secondary:* i) To demonstrate that a fixed dose combination of telmisartan 80 mg plus HCTZ 12.5 mg is superior to telmisartan 80 mg alone in patients,

	who fail to respond adequately to telmisartan 80 mg monotherapy, in lowering seated trough systolic blood pressure after eight weeks of treatment. ii) To demonstrate that a fixed dose combination of telmisartan 80 mg plus HCTZ 12.5 mg is superior to telmisartan 80 mg alone in patients, who fail to respond adequately to telmisartan 80 mg monotherapy, in lowering standing trough DBP and SBP after eight weeks of treatment. iii) To monitor safety through phys. examinations, laboratory parameters, 12-lead ECG and adverse events.
Methodology:	All patients entered a one-week screening phase prior to starting the eight-week open-label T80 mg period. At end of four weeks only patients who failed to respond to T80 mg (DBP ≥ 90 mm Hg) continued the treatment with T80 mg for another four weeks. At the end of eight weeks, only patients who failed to respond to T80 mg (DBP ≥ 90 mm Hg) were randomized, double-blind, to receive either T80 mg alone or the fixed dose combination of T80 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 baseline and at the final visit.
No. of subjects:	
planned:	Entered: 340 subjects (170 in each group).
actual:	Enrolled: 699 subjects. Entered/randomized: 345 subjects (175 in TELM80/HCTZ12.5 group, 170 in TELM80 group). Completed: 329 subjects (168 in TELM80/HCTZ12.5 group, 161 in TELM80 group) Safety: 345 subjects (175 in TELM80/HCTZ12.5 group, 170 in TELM80 group) Full Analysis Set (FAS): 342 subjects (173 in TELM80/HCTZ12.5 group, 169 in TELM80 group) Per-protocol set (PPS): 295 subjects (154 in TELM80/HCTZ12.5 group, 141 in TELM80 group)
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 fail to respond adequately to telmisartan monotherapy.
Test product:	telmisartan/hydrochlorothiazide fixed dose combination with matching placebo
dose:	80 mg/12.5 mg once daily
mode of admin.:	tablet, p.o.

batch no.:	active: B040050B placebo: B040050B
Duration of treatment:	8 weeks
Reference therapy:	telmisartan with matching placebo
dose:	80 mg
mode of admin.:	tablet, p.o.
batch no.:	active: B040050B placebo: B040050B

Criteria for evaluation:

Efficacy:

Primary efficacy variable: change from baseline in mean seated trough DBP after 8 weeks of randomized treatment or at last trough observation during the double-blind phase.

Secondary Effiacy variable:

i) Change from baseline in mean seated trough SBP after 8 weeks of randomized treatment or at last trough observation during the double-blind phase.

ii) Change from baseline in mean standing trough DBP and SBP after 8 weeks of randomized treatment or at last trough observation during the double-blind phase.

iii) The percentage of patients responding to the treatment (as measured by in clinic trough cuff blood pressure after 8 weeks of randomized treatment or at last trough observation during the double-blind phase) based on mean seated trough cuff measurement s defined as

DBP Control: Mean seated DBP < 90mmHg at trough

DBP Response: Mean seated DBP< 90mmHg at trough and/or a change from baseline of ≥10mmHg

SBP Response: Mean seated SBP< 140mmHg at trough and/or a change from baseline of ≥10mmHg

BP categories:

- Optimal: SBP <120 mmHg and DBP <80 mmHg.
- Normal: SBP <130 mmHg and DBP <85 mmHg and not 'optimal'.
- High-normal: SBP <140 mmHg and DBP <90 mmHg and not ('optimal' or 'normal').
- High: SBP ≥140 mmHg or DBP ≥90 mmHg.

Statistical methods:

The SAFETY set was used for all tabulations related to safety, especially for the reporting of AEs.

The primary analyses and secondary analyses were based on FAS. If FAS and PPS differed by more than 10% in size, the primary analysis was to also be carried out for the PPS. All patients were assigned to treatment group based on their randomisation code.

Standard descriptive statistical parameters were to be calculated for continuous variables if not otherwise specified, included N, Mean, Standard Deviation (SD), Min (Minimum), Q1 (25% percentile), Median, Q3 (75% percentile), and Maximum. All calculated statistics were to be given with one more decimal digit than the raw measurement value.

Frequency tables with percentages were to be displayed for category variables. Percentages were to be reported with one decimal.

All efficacy analyses were to be performed on the FAS population using the LOCF method of data imputation. For the primary efficacy endpoints, missing data were to be replaced as described in section 9.7.1.5. The primary endpoint analysis on PP population was to depend on the BRPM decision.

All statistical tests were to be calculated two-sided of significance at an α-value of 0.05. The precise model to be used for primary endpoint was as follows:

$$dijk = c\ yijkB + \mu + \tau i + \beta j + \varepsilon ijk$$

To assess whether the treatment effect was homogeneous across centres, a further model that included the treatment-by-centre interaction was to be explored.

Subgroup analyses were planned for sex and age (< 65 years vs. >=65 years). The primary model from above with the addition of "subgroup", and including a term for the interaction subgroup-by-treatment was to be used.

The secondary analyses were to be based on FAS population using LOCF analysis.

The same model as described above for the primary endpoint was to be used for secondary endpoints that include the change from baseline in mean seated trough SBP as well as in mean standing trough DBP and SBP. The same pooling rules for centres as for the primary endpoints were to be used.

Other secondary efficacy endpoints characterizing categories that included DBP control and response, SBP response and BP high normality classes were to be summarized by treatment group for frequency and percentages and compared by the Cochran-Mantel-Haenszel test adjusting for center.

Adverse events, laboratory data, physical examinations, ECG, orthostatic blood

	pressure were summarized for safety evaluation.
Safety:	Reports of adverse events, and laboratory assessments, physical examinations, and ECG at screening, at baseline and at end of DB phase.

SUMMARY – CONCLUSIONS

Demographic and Baseline characteristics:

A total of 699 subjects were enrolled in this study and 345 patients were randomized into one of TELM80/HCTZ12.5 and TELM80 groups and treated (175 in TELM80/HCTZ12.5 group, 170 in TELM80 group). 16 subjects prematurely discontinued from this study in total (7 in TELM80/HCTZ12.5 group, 9 in TELM80 group), due to adverse events, lack of efficacy or administrative reason.

Out of 345 patients randomized, there were 105 male and 70 female in TELM80/HCTZ12.5 group, 105 male and 65 female in TELM80 group. All were Asian. The mean age (±SD) was 51.7±9.4 years and 51.2±9.6 years, respectively, in TELM80/HCTZ12.5 group and TELM80 group. The mean height was 167.1±7.5 cm and 167.1±8.3 cm, respectively, in TELM80/HCTZ12.5 group and TELM80 group.The mean weight was 71.9±11.0 kg and 72.6±11.0 kg, respectively, in TELM80/HCTZ12.5 group and TELM80 group. The mean body mass index was 25.7±3.4 kg/m^2 and 25.9±3.0 kg/m^2, respectively, in TELM80/HCTZ12.5 group and TELM80 group.

The mean sitting diastolic blood pressure, sitting systolic blood pressure, standing diastolic blood pressure and standing systolic blood pressure was 95.8±4.3 mmHg, 145.8±12.2 mmHg, 96.4±7.1 mmHg and 145.8±12.8 mmHg, respectively, in TELM80/HCTZ12.5 group, and was 95.9±4.6 mmHg, 144.4±12.6 mmHg, 97.2±6.9 mmHg and 144.7±13.8 mmHg, respectively, in TELM80 group at visit 4.

The demographics were comparable between two treatment groups ($p>0.05$), except for patient distribution of smoke habit ($p=0.0453$).

Efficacy results:

The majority of 345 subjects were well compliant with the planned schedule over the study by compliance calculation within 80%-120% (329 subjects in total, with 168 in the TELM80/HCTZ12.5 group and 161 in the TELM80 group, respectively) at last visit.

The mean (±SD) change from baseline in sitting DBP was –10.1±6.7 mmHg in TELM80/HCTZ12.5 group and –7.7±8.1 mmHg in TELM80 group, with the mean sitting DBP of 85.6±7.9 mmHg in TELM80/HCTZ12.5 group and 88.2±9.5 mmHg in TELM80 group at last visit, respectively. The difference of the mean change from baseline in sitting DBP had statistical significance between groups at endpoint ($p=0.0017$). Results from PP population were similar to that of FAS population.

There was no center by treatment interaction observed in sitting DBP at end of the study (p>0.05).

The mean (±SD) change from baseline in sitting SBP at trough was –14.2 ±11.4 mmHg in TELM80/HCTZ12.5 group and –7.4±12.5 mmHg in TELM80 group, with the mean sitting SBP of 131.6±13.5 mmHg in TELM80/HCTZ12.5 group and 136.9±14.8 mmHg in TELM80 group at last visit, respectively. The difference of the mean change from baseline in sitting SBP had statistical significance between groups at endpoint (p<0.0001).

The mean (±SD) change from baseline in standing DBP at trough was –8.7 ±7.6 mmHg in TELM80/HCTZ12.5 group and –7.3±8.4 mmHg in TELM80 group, with the mean standing DBP of 87.7±9.5 mmHg in TELM80/HCTZ12.5 group and 89.9±10.5 mmHg in TELM80 group at last visit, respectively. The difference of the mean change from baseline in standing DBP had statistical significance between groups at endpoint (p=0.0350).

The mean (±SD) change from baseline in standing SBP at trough was –12.9 ±11.3 mmHg in TELM80/HCTZ12.5 group and –7.0±12.3 mmHg in TELM80 group, with the mean standing SBP of 132.8±14.1 mmHg in TELM80/HCTZ12.5 group and 137.7±15.3 mmHg in TELM80 group at last visit, respectively. The difference of the mean change from baseline in standing SBP had statistical significance between groups at endpoint (p<0.0001).

The percentage of patients responding to the treatment in trough cuff DBP measurement was 74.6% (129 subjects) in TELM80/HCTZ12.5 group and 59.2% (100 subjects) in TELM80 group at endpoint, respectively. The inter-group difference was statistically significant (p=0.0016).

The percentage of patients responding to the treatment (Delta >= 10 mmHg) in trough cuff SBP measure was 83.8% (145 subjects) in TELM80/HCTZ12.5 group and 66.9% (113 subjects) in TELM80 group at endpoint, respectively. The inter-group difference was statistically significant (p=0.0001).

In addition, calculated by Delta >= 20 mmHg, the percentage of patients responding to the treatment in trough cuff SBP measure was 74.6% (129 subjects) in TELM80/HCTZ12.5 group and 61.5% (104 subjects) in TELM80 group at endpoint, respectively. The inter-group difference was statistically significant (p=0.0060).

For subjects in FAS population, the percentage of patients classified as optimal, normal, high normal or high blood pressure was 9.2%, 25.4%, 28.3% or 37.0%, respectively, in TELM80/HCTZ12.5 group and 4.1%,16.0%, 24.9%, or 55.0%, respectively, in TELM80 group at end of study. The inter-group difference was statistically significant (p=0.0086).

A marginally significant age by treatment interaction was observed for sitting

	DBP reduction (p=0.0682) at end of the study. This may indicate that the difference between treatments is only seen within younger patients. The inter-group difference (-2.95 mmHg) of mean sitting DBP was significant in <65 years old subgroup (p=0.0004) in favor of TELM80/HCTZ12.5 treatment at end of the study. While, the inter-group difference (1.70 mmHg) of mean sitting DBP was not significant in >= 65 years old subgroup (p>0.05). However, the number of patients in the elderly group was too small to draw any conclusion. There was no significant sex by treatment interation observed for sitting DBP reduction at end of the study (p>0.05) indicating that the advantage of TELM80/HCTZ12.5 over TELM80 was similar in males and females. The inter-group difference (-2.25 mmHg) of mean sitting DBP was significant in male subgroup (p=0.0288) in favor of TELM80/HCTZ12.5 treatment at end of the study. The inter-group difference (-2.85 mmHg) of mean sitting DBP was also significant in female subgroup (p=0.0267).
Safety results:	There were totally 94 subjects (27.2%) reported adverse events during the study. Among which, 35 subjects (20.0%) in TELM80/HCTZ12.5 group and 28 subjects (16.5%) in TELM80 group reported adverse events during double blind period, and 1 subject (0.3%) reported adverse event during post-treatment period. Classified by worst intensity of adverse events, number of subjects experienced mild, moderate or severe adverse events was 29 (16.6%), 7 (4.0%) or 1 (0.6%) in TELM80/HCTZ12.5 group, and was 24 (14.1%), 4 (2.4%) or 1 (0.6%) in TELM80 group, respectively, during double blind period. 1 subjects experienced mild adverse events at post-treatment period. The most frequently reported adverse events during double blind were laboratory test findings (11 subject, 6.3%), nerve system disorders (6 subjects, 3.4%), Metabolism and nutrition disorders (4 subjects, 2.3%), Infections and infestations (4 subjects, 2.3%)and Cardiac disorders (4 subjects, 2.3%) in TELM80/HCTZ12.5 group, and were laboratory test findings (9 subject, 5.3%), Metabolism and nutrition disorders (6 subject, 3.5%), Gastrointestinal disorders (4 subject, 2.4%) and Infections and infestations (3 subject, 1.8%) in TELM80 group. As to the relationship to study dosing at the discretion of investigators, there were 6 subjects reported adverse events related to study dosing in TELM80/HCTZ12.5 group during double blind period. Subject [redacted] experienced mild blood bilirubin increased and mild urine bilirubin increased. Subject [redacted] experienced mild blood uric acid abnormal. Subject [redacted] experienced mild protein urine present. Subject [redacted] experienced mild hyperkalaemia and mild hyperuricaemia. Subject [redacted] experienced mild hypokalaemia. Subject [redacted] experienced mild rash. There were also 6 subjects reported adverse events related to study dosing in

TELM80 group during double blind period. Subject [redacted] experienced mild blood bilirubin increased. Subject [redacted] experienced mild blood uric acid increased. Subject [redacted] experienced mild blood urine. Subject [redacted] experienced mild hyperuricaemia. Subject [redacted] experienced mild dysphonia. Subject [redacted] experienced severe hpertension (worsening of current hypertension).

There were 3 subjects experienced serious adverse events during double blind period (all in TELM80/HCTZ12.5 group), including one subject experienced moderate coronary artery disease, one subject experienced moderate ischaemic stroke, and one subject experienced severe Uterine haemorrhage. All of the three subjects discontinued from study dosing. The adverse events of coronary artery disease and Uterine haemorrhage recovered, while the adverse event of ischaemic stroke led to sequelae. These 3 SAEs were not related to the study medcations as judged by the investigators.

There were no deaths reported during the study.

At the end of treatment, the possible clinically significant abnormalities on Haemetology, Blood chemistry parameters and Urinalysis were observed in TELM80/HCTZ12.5 group and TELM80 group.

There were very few clinically relevant findings in physical examination, 12-lead ECG or orthostatic blood pressure change at end of the study. In TELM80/HCTZ12.5 group, there was 1 subject reported new/worsening ECG findings, no subject reported clinically relevant physical examination or orthostatic blood pressure findings at end of the study. In TELM80 group, there were 2 subjects reported new/worsening physical examination findings and 2 subjects reported new/worsening ECG findings, no subject reported clinically relevant orthostatic blood pressure findings.

Conclusions:

In conclusion, results of this study suggest that treatment with telmisartan 80 mg and hydrochlorothiazide 12.5 mg fixed dose combination was more effective than treatment with telmisartan 80 mg monotherapy, and was safe and well tolerated in patients not responsed to monotherapy. Telmisartan 80 mg and hydrochlorothiazide 12.5 mg fixed dose combination can be used in Chinese hypertensive patients who fail to respond adequately to Telmisartan 80 mg monotherapy.