Clinical Study Synopsis for Public Disclosure

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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.

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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.

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2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Micardis®, Motens®				
Name of active ingredient: Telmisartan, Lacidipine		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 05 Dezember 2002	**Number:** 502.378	**Study period (years):** 09/01 – 03/02		

Title of study:	A double-blind, randomised, placebo controlled, 6 parallel groups study to assess the influence of telmisartan (40 mg or 160 mg), lacidipine (4 mg or 6 mg) and their combination (telmisartan 40 mg and lacidipine 4 mg) p.o. once daily for seven days on the QT interval of the ECG in healthy male and female volunteers
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma KG, Germany
Publication (reference):	Data of the trial have not been published
Clinical phase:	I
Objectives:	Assessment of the influence of telmisartan, lacidipine and their combination on the QTc interval of the ECG
Methodology:	Randomised, double-blind, placebo controlled, 6 parallel groups
No. of subjects entered:	
total:	149
each treatment:	25: telmisartan 40 mg 25: telmisartan 160 mg 24: lacidipine 4 mg 26: lacidipine 6 mg 25: lacidipine 4 mg and telmisartan 40 mg 24: placebo
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age 21 – 50 years, BMI: 18.5 – 29.9 kg/m^2
Test product:	Telmisartan tablets
dose:	40 mg and 160 mg
mode of admin.:	p.o.
batch no.:	90002690, 9000270
Duration of treatment:	Seven days for each treatment
Reference therapy:	Lacidipine tablets; placebo matching to telmisartan tablets 40 mg and 80 mg and to lacidipine tablets 2 mg
dose:	4 or 6 mg (lacidipine), N/A (placebo)
mode of admin.:	p.o.
batch no.:	115307, 01035, 9000276, 9000277

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Criteria for evaluation:

Efficacy:	ECG-parameters, especially QT-interval length PK: AUC_{day1}, AUC_{ss}, $C_{max,day1}$ and $C_{max,ss}$, t_{max}, $t_{max,ss}$, $C_{min,ss}$
Safety:	Blood pressure, heart rate, ECG, adverse events, laboratory tests
Statistical methods:	Analysis of covariance

SUMMARY – CONCLUSIONS:

Efficacy results (see section 11.4.1):

The primary aim of this study was to investigate the effect of telmisartan and lacidipine each alone and in combination on ventricular repolarisation, expressed by the length of the QT interval of the ECG and derived parameters.

The frequency correction according to Fridericia, QTcF, turned out to adequately describe the heart frequency dependence of the QT interval in the population of this trial. This was expected before the trial, and no reason was seen from the blinded results of this trial to change the plan to use QTcF as primary parameter.

In the primary endpoint, the adjusted treatment group mean change from baseline to day 7 in weighted mean QTcF, only slight differences of –2.6 ms to +1.6 ms compared to placebo were seen. The same holds true for the respective change from baseline to day 1, where differences of –2.4 ms to +0.2 ms compared to placebo were seen. Both on day 1 and day 7, for the three treatments containing telmisartan (telmisartan 40 mg, telmisartan 160 mg and telmisartan 40 mg with lacidipine 4 mg) a mean change lower than in the placebo group was seen. For the lacidipine 4 mg group on day 1 a smaller change than for placebo was observed (-1.0 ms), whereas on day 7 a higher change than for placebo could be seen (+1.6 ms). For the lacidipine 6 mg group, higher changes compared to placebo were seen on both day 1 (0.2 ms) and day 7 (1.5 ms).

Altogether, these slight changes do not show any dose dependency for any of the two drugs nor any consistency pointing to a possible QTcF interval prolongation due to the drugs or their combination. The increase of the primary endpoint in the placebo group of 3.6 ms indicates the range in which the primary endpoint can change without drug influence.

The changes did not vary significantly between males and females across treatment groups both for day 1 and for day 7.

Also for the secondary parameter maximum QTcF change from baseline to day 7 and to day 1, all changes are between -2.9 ms and +1.9 ms compared to placebo. No change was significant, an increase compared to placebo was seen only in the treatment groups lacidipine 4 mg and lacidipine 6 mg and only on day 7.

Also the analysis of outliers does not point to a drug-dependent increase in QTcF. No subject showed an increase of more than 30 ms or more than 15% in their change to baseline weighted mean QTcF on day 1 or 7.

No new onset of QTcF greater than 500 ms occurred at any time on any treatment, maximum QTcF on day 1 as well as on day 7 was less than 450 ms with each subject in each treatment group. Maximum QTcF changes from baseline to day 1 or day 7 were less than 30 ms with two exceptions: there was one maximum change from baseline of 33.3 ms in the treatment group telmisartan 40 mg with lacidipine 4 mg on day 1, and one

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maximum change from baseline of 32.0 ms in the treatment group lacidipine 6 mg on day 7. These extreme changes are only slightly above the limit of 30 ms, and the rate of two such outliers among 2160 post-dose ECGs on days 1 and 7 (15 timepoints, seven on day1 and eight on day 7, times 144 subjects) is very low.

Also for the parameters QTcB and QT uncorrected, no new onset of values greater than 500 ms occurred at any time on treatment. The results of other ECG intervals (PQ, QRS) did not reveal any relevant drug related changes.

The results of primary and secondary endpoints do not suggest any drug dependent increase of weighted mean QTcF, maximum QTcF, nor could any relevant extremes be seen. No subject's treatment had to be discontinued due to a QT interval increase. Both drugs and their combination in the doses investigated did not reveal any relevant or significant impact on any of the QT interval parameters observed.

Pharmacokinetic results:

Telmisartan plasma concentrations were analysed by enzyme-linked immunosorbent assay (ELISA) (lower limit of quantification 0.3 ng/mL). Lacidipine plasma concentrations were determined by HPLC-MS/MS (lower limit of quantification 0.02 ng/mL).

The evaluation of plasma concentrations and pharmacokinetic parameters revealed that co-administration of telmisartan and lacidipine had no effect on the pharmacokinetics of either compound, respectively. Plasma concentrations and pharmacokinetic parameters were within the range expected for these compounds. As was observed in previous studies [U99-1390, U93-0014], both telmisartan and lacidipine showed a greater than proportional increase in bioavailability with increasing doses.

Safety results:

AEs were analysed according to the study medication the subject received at onset of the AE.

In total, 96 subjects (64.4%) out of 149 subjects participating in the study experienced adverse events.

Headache was the AE occurring in most subjects (51 subjects. 34.2%). Other AEs occurring in more than 5% of the subjects were feeling hot, (20 subjects, 13.4%), fatigue (16 subjects, 10.7%), and nasopharyngitis (14 subjects, 9.4%).

Eighty-nine (89) out of 149 subjects experienced AEs with worst intensity mild, 21 subjects experienced AEs with worst intensity moderate. One subject ([redacted] on lacidipine 6 mg) experienced headache of severe intensity of 90 minutes duration in the evening of day 4. There was no other AE of severe intensity.

One adverse event was treated and reported as serious adverse event because permanent sequelae could not be excluded: one subject experienced a lesion of the medianus nerve in the lower left arm, probably due to venous cannulation for blood sampling. Though probably related to the study procedures, there is no reasonable drug relationship of this SAE.

There were no other serious or significant AEs during this study.

Comparison of the number of subjects with AE between the treatment groups shows that this number is lowest (but anyhow 45.8%) in the placebo group, somewhat higher in the two telmisartan groups with less subjects

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experiencing AEs in the 160 mg telmisartan group (48.0%) than in the 40 mg telmisartan group (56.0%), more subjects with AEs in the two lacidipine groups (62.5% in the 4 mg lacidipine group and 76.9% in the 6 mg lacidipine group. The highest rate is seen in the combination group (40 mg telmisartan and 4 mg lacidipine) with 80.0% of the subjects experiencing at least one AE.

From the pattern of adverse events observed in this trial no new conclusions can be drawn for the safety of either or both medications combined, if used as anti-hypertensive treatment or for influencing the renin-angiotensin system. The high rate of AEs in all treatment groups including the placebo group demonstrates the thorough documentation of AE in this phase I setting. The pattern of AEs is expected to be different in a hypertensive population, and several AEs may be avoided by dose titration.

Conclusions:

The primary aim of this study was to investigate the effect of telmisartan and lacidipine each alone and in combination on ventricular repolarisation, expressed by the length of the QT interval of the ECG and derived parameters.

For this purpose, six different treatments were given in this double blind, randomised trial: telmisartan 40 mg, telmisartan 160 mg, lacidipine 4 mg, lacidipine 6 mg, telmisartan 40 mg with lacidipine 4 mg (combination treatment) and placebo. Each treatment was given once daily over 7 days. 43 ECGs were to be evaluated in each subject, eight ECGs each on day –2 and day –1 (the two days preceding first treatment) as well as on days 1 and 7 of treatment, two ECGs each on days 2 to 6 of treatment and one ECG on day 8.

The frequency correction according to Fridericia, QTcF, turned out to adequately describe the heart frequency dependence of the QT interval in the population of this trial and thus was used as primary parameter as planned.

The analysis of the primary endpoint (ANCOVA for weighted mean QTcF change from baseline to day 7) revealed only slight differences of –2.6 ms to +1.6 ms compared to placebo. The same holds true for the respective change from baseline to day 1, where differences of –2.4 ms to +0.2 ms compared to placebo were seen.

Summarising, the results of primary and secondary endpoints do not suggest any drug dependent increase of weighted mean QTcF, maximum QTcF, nor could any relevant outliers be seen in QTcF, QTcB or uncorrected QT. No subject's treatment had to be discontinued due to a QT interval increase. Both drugs and their combination in the doses investigated did not reveal any relevant or significant impact on any of the QT interval parameters observed.

Telmisartan and lacidipine plasma concentrations covered the range expected for these compounds. There were no signs of medication errors since adequate drug exposure was shown for all subjects. The evaluation of plasma concentrations and pharmacokinetic parameters revealed that co-administration of telmisartan and lacidipine had no effect on the pharmacokinetics of either compound, respectively.