Boehringer Ingelheim

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**.

Name of company: Boehringer Ingelheim International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: MICARDIS®			
Name of active ingredient: telmisartan		**Page: 1 of 4**	
Report date: 12 April 2006	**Trial-Number:** 502.469	**Study period (dates):** 22 FEB 2005-14 OCT 2005	**Date of Revision:** 10 October 2006

Title of study:	A randomised, double-blind, placebo-controlled, parallel group, 16-week MICARDIS® (160 mg) tablets, proof-of-concept study, evaluating insulin sensitivity in overweight or obese, non-diabetic, normotensives, using the oral glucose tolerance test, with a clamp sub-group
Investigator:	[redacted]
Study centers:	Multicentre study
Publication (reference):	Data of this study has not been published
Clinical phase:	II
Objectives:	The objective of this study was to determine whether MICARDIS® (telmisartan 160 mg) improved insulin sensitivity in overweight or obese, non-diabetic, normotensive subjects.
Methodology:	Prospective, randomised, double-blind, placebo-controlled, parallel group, forced up-titration study using a 3-hour oral glucose tolerance test (OGTT) with a hyperinsulinemic euglycemic clamp sub-group to measure insulin sensitivity.
No. of subjects:	
planned:	entered: 120
actual:	enrolled: 309 MICARDIS® 160 mg: entered: 69 treated: 69 analysed (for primary endpoint): 65 PLACEBO: entered: 69 treated: 69 analysed (for primary endpoint): 64
Diagnosis and main criteria for inclusion:	Overweight or obese (BMI ≥28), sedentary lifestyle, waist circumference ≥40 inches (102 cm) in men or ≥35 inches (89 cm) in women, non-diabetic (fasting glucose ≤126 mg/dL and HbA_{1C} ≤6.5%), triglycerides ≥150 and ≤500 mg/dL, and normotensive (≥110/64 and ≤140/90 mmHg).
Test product:	MICARDIS®
dose:	80 mg for 2 weeks; forced up-titration to 160 mg (2x80 mg) for 14 weeks, once-daily
mode of admin.:	Tablets p.o.
batch no.:	United States and Canada Formula Number 1459-01; Lot Number PD-2505 Europe Formula Number BIRB 277 SE TA 1 2A 1I; Lot Number 403705

Duration of treatment:	16 weeks
Reference therapy:	Placebo (matching)
dose:	N/A
mode of admin.:	Tablets p.o.
batch no.:	United States and Canada Formula Number 1461-01; Lot Number PD-2504 Europe Formula Number BIRB 277 SE TA 1 2A 0I; Lot Number 403709

Criteria for evaluation:

Efficacy:

Primary endpoint:

Change from baseline to the end of study (16 weeks) in insulin sensitivity index calculated as the composite index from a 3-hour oral glucose tolerance test (OGTT).

Secondary endpoints:

Changes from baseline to the end of study (16 weeks) in:

- Glucose disposal rates (R_d): mean glucose infusion rates required to maintain euglycemia over the final 30 minutes of both the low and high dose insulin infusion during a 2-step hyperinsulinemic euglycemic clamp procedure),
- Insulin sensitivity index calculated as R_d/I based on the clamp procedure;
- Insulin sensitivity index calculated from the OGTT results using a minimal model technique;
- Insulin secretion capacity using C-peptide ($\Delta_{0\text{-}30\ minutes}$),
- Fasting serum insulin and plasma glucose,
- Area under the curve (AUC) for glucose and insulin (OGTT),
- Ratio of $AUC_{glucose}$ divided by $AUC_{insulin}$ (OGTT),
- Circulating lipids [triglycerides, total cholesterol, high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC) and free fatty acids (FFA)],
- Inflammatory markers (adiponectin and highly sensitive C-reactive protein-clamp centres only).

Safety:

Evaluation of adverse events (AEs); changes in physical exam; blood pressure, pulse rate, ECG, and routine laboratory values.

Statistical methods: Analysis of covariance (primary analysis); Wilcoxon rank sum test stratified by centre; descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy results:

For the insulin sensitivity index of SI(Composite) based on the 3-hour OGTT, no significant difference (p=0.8217) was found between the treatment effects of telmisartan 160 mg and placebo (adjusted mean changes from baseline of 0.19 and 0.30, respectively) when analyzing the per-protocol analysis set. The same was true when analyzing the full analysis set (p=0.8312).

There were also no significant treatment effects found for the other insulin sensitivity indexes based on the OGTT of SI(MinModel), SI(QUICKI), and SI(HOMA), or for the other secondary endpoints based on the OGTT of fasting plasma glucose, fasting serum insulin, change from 0-30 minutes in C-peptide, AUC(Glucose), AUC(Insulin), and the ratio of AUC(G)/AUC(I).

When evaluating treatment effects on the secondary endpoints based on the hyperinsulinemic euglycemic clamp procedure performed in a subgroup of subjects, no significant differences were found between the adjusted mean changes for subjects treated with telmisartan 160 mg or placebo for either the low and high dose insulin glucose disposal rates or the low and high dose insulin measures of insulin sensitivity, SI(Clamp). As well, even though non-significance was not unexpected due to the small number of subjects involved in the clamp sub-study, no consistent positive treatment effect on these endpoints relating to the clamp procedure was noted for subjects treated with telmisartan 160 mg.

Additionally, when evaluating treatment effects on the various measures of insulin sensitivity based on both the OGTT and clamp procedure results for various subgroups of subjects (i.e. based on their baseline SI(Composite) or baseline glucose disposal rates; eliminating subjects with a weight change over the course of the study of ≥3%; or eliminating subjects treated with telmisartan that had questionable compliance with study drug based on their results of direct rennin), no single reason was found that would explain the overall non-significance between telmisartan 160 mg and placebo in increasing insulin sensitivity.

Safety results:

The mean duration of treatment exposure was comparable across the treatment groups (107.7, and 110.4 days for placebo and telmisartan, respectively). Sixty-one (44.2%) of the 138 randomised subjects reported one or more adverse events during the course of the study of which five (3.6%) subjects prematurely discontinued: two (2.9%) from placebo and three (4.3%) from telmisartan. The overall incidence of adverse events was comparable across the treatment groups (46.4% placebo and 42.0% telmisartan). Primarily the AEs in each treatment group were of mild or moderate intensity. There were a total of four (2.9%) subjects who experienced AEs of severe intensity: two (2.9%) subjects in the placebo group, one (1.4%) while on the initial dose (telmisartan 80 mg) and, one (1.5%) on the target dose (telmisartan 160 mg), of which the two active treatment subjects discontinued the study.

Adverse events were similar between both treatment groups. Events of bronchitis, nasopharyngitis, dyspepsia, and rash were greater than 2% in the placebo group with none of the above events reported in the telmisartan group. Pneumonia, paraesthesia, and dyspnoea were reported greater than 2% in the telmisartan group. None of these events were reported in the placebo group. Drug related events were similar between both groups (10.1% placebo and 11.6% telmisartan). Drug related events reported in two or more subjects included upper abdominal pain (2) and diarrhea (2) in the placebo arm and dizziness (2), paraesthesia (2), nausea (2) and fatigue (2) in the telmisartan arm.

One subject reported SAEs (diarrhea and pneumonia) during the target dose (telmisartan 160 mg) phase of the study not considered drug related by the Investigator or Clinical Monitor. This subject also experienced non-serious events of dehydration deemed as not drug related and acute renal failure, hyperkalemia and nausea, which were deemed as possibly drug related following study drug rechallenge. The subject recovered from all adverse events and prematurely discontinued from the study.

Conclusions:

Telmisartan at a dose of 160 mg was safe and well tolerated. The safety profile was similar to the 80 mg dose that is used clinically for the treatment of hypertension.

Based on the results of this study, conducted in non-diabetic and non-hypertensive overweight and/or obese subjects, whose insulin resistance level was not an entry criterion, telmisartan could not be shown to have an effect on insulin sensitivity as assessed by the oral glucose tolerance test or the hyperinsulinemic euglycemic clamp. Additional studies will be required to assess if an effect on insulin resistance can be demonstrated in other patient populations.