This Summary of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can't be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2 SYNOPSIS

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Title of the study:
Efficacy and Safety of Zofenopril + Hydrochlorothiazide Combination vs. Irbesartan + Hydrochlorothiazide Combination in Metabolic Syndrome Patients with Essential Hypertension not Controlled by Previous Monotherapy.

Study Centres and Principal Investigator(s):

[redacted]

SYNOPSIS (cont.)

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Study Centres and Principal Investigator(s) (cont.d):

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Publication (reference):			
Studied period (years): **2010-2012**	**Date of first enrolment:** **14JAN10** **Date last visit completed:** **24JAN12**		**Phase of development:** **III**

Objectives:
Objectives of this study were to evaluate the antihypertensive efficacy on office diastolic blood pressure of the fixed combination Zofenopril + hydrochlorothiazide as respect to the Irbesartan + hydrochlorothiazide fixed combination, in metabolic syndrome patients with essential hypertension not controlled by a previous monotherapy and to compare safety of the treatments under study.

Methodology:
Multicenter, randomized, double-blind, over encapsulation, active controlled, two parallel groups, phase III study.

Number of subjects (planned and analysed):
A total of four-hundred and eighty-two subjects have been planned to be screened, in order to have 410 evaluable subjects, in 41 Italian and Romanian clinical sites. A total of 721 subjects were screened and 482 randomised (safety population). Out of them, 466 entered in the FAS population and thus in the efficacy statistical analyses.

Diagnosis and main criteria for inclusion and exclusion:
Male or female Caucasian outpatients aged ≥ 18 years with diagnosis of essential hypertension according to Guidelines of European Society of Cardiology; fasting plasma glucose ≥ 100mg/dL or on drug treatment for elevated glucose; one or more of the following criteria: 1) waist circumference ≥ 102 cm in men and ≥ 88 cm in women, 2) serum triglycerides ≥ 150 mg/dL or on drug treatment (Statins, Omega 3 and Fibrates) for elevated triglycerides, 3) HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women or on drug treatment for reduced HDL-C; continuous treatment with the same single antihypertensive drug (single active pharmaceutical ingredient) at least for 4 weeks before inclusion in the study; able and willing to comply with study procedures; written informed consent**.**

Moreover, subjects had not to meet any of the following exclusion criteria: serum level of HDL cholesterol < 35 mg/dL and/or triglycerides > 1000 and/or LDL-C > 190 mg/dL; malignant or secondary hypertension; systolic isolated hypertension; orthostatic hypotension (difference between mean sitting and standing SBP ≥ 20 mmHg); heart failure requiring medical treatment; myocardial infarction in the 6 months prior to enrolment; cerebrovascular events (including stroke or transient ischemic attack) in the previous 6 months; haemodynamically significant valvulopathy; hereditary/idiopathic angioedema; history of angioedema associated with previous ACE-inhibitor therapy; liver pathology (AST or ALT > 3 times greater than normal upper limit or total serum bilirubin > 1.5 times greater than upper limit); bilateral renal arterial stenosis, or unilateral for patients with a single kidney; renal insufficiency (creatininemia > 200 µmol/L or 2 mg/dL); hypokalemia (< 3.5 mEq/L) or hyperkalemia (> 5.0 mEq/L) at least at two haematological examinations (if the patient presents at baseline hypo or hyperkalemia, this value had to be confirmed either by a previous examination or by a new one within 3 days); hyponatremia (< 136 mEq/L); hypernatremia (Na > 145 mEq/L); hypercalcemia: (serum Ca) + [(4 – serum albumin) x 0,8] > 10,2 mg/dL; hyperuricemia (uric acid > 7 mg/dL); patients receiving dialysis; hereditary galactose intolerance, Lapp lactase deficiency or glucose galactose malabsorption; other severe concurrent diseases (cancer, AIDS, liver disease, etc.); positive history for renal transplantation; dementia, psychosis, alcoholism (> 350 g ethanol/week) or chronic abuse of medicines, drugs or psychoactive substances, introduction of concurrent therapies among those not permitted and which could not be suspended without harm to the patient; hypersensitivity or contraindications to use of the product under study; history of undesired side effects with ACE-inhibitors, AT1-antagonists or diuretics; current treatment with any antihypertensive agents that could not be safely stopped (Investigator's decision) the day before the randomisation visit (V0); participation in other clinical trials in the previous 4 months; conditions which in the Investigator's opinion might interfere with the study's execution or due to which the patient should not participate for safety reasons; risk of low patient cooperation; pregnant or lactating females; females of childbearing potential not using adequate contraceptive

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Diagnosis and main criteria for inclusion and exclusion (cont.d):
precautions such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence or vasectomised partner.

Test product, dose, mode of administration, batch N°:

- Zofenopril 30 mg + hydrochlorothiazide 12.5 mg fixed dose combination over-encapsulated in DBAA capsules suitable to keep the blinding, manufactured by A. Menarini MMLS – Firenze, to be taken once a day after breakfast with a glass of water, from week 0 to 8, Each dose consisted of one capsule.
- Zofenopril 30 mg + hydrochlorothiazide 12.5 mg fixed dose combination over-encapsulated in DBAA capsules suitable to keep the blinding and Zofenopril 30 mg over-encapsulated in DBAA capsules suitable to keep the blinding manufactured by A. Menarini MMLS – Firenze to be taken once a day after breakfast with a glass of water, from week 9 to 24. Each dose consisted of two capsules, to be taken together.

Batch CTC0930 – Expiry date: DEC 2011; batch CTM0909 - Expiry date: DEC 2012; (Zofenopril 30 mg + hydrochlorothiazide 12.5 mg capsules); Batch CTC0919 – Expiry date DEC2011; batch CTL0930 – Expiry date AUG2012 (Zofenopril 30 mg capsules).

Reference therapy, dose, mode of administration, batch N°:

- Irbesartan 150 mg + hydrochlorothiazide 12.5 mg fixed dose combination over-encapsulated in DBAA capsules suitable to keep the blinding manufactured by A. Menarini MMLS – Firenze, to be taken once a day, after breakfast with a glass of water from week 0 to 8, Each dose consisted of one capsule.
- Irbesartan 150 mg + hydrochlorothiazide 12.5 mg fixed dose combination over-encapsulated in DBAA capsules suitable to keep the blinding and Irbesartan 150 mg over-encapsulated in DBAA capsules suitable to keep the blinding, manufactured by A. Menarini MMLS – Firenze to be taken once a day after breakfast with a glass of water, from week 9 to 24, Each dose consisted of two capsules, to be taken together

Batch CTD0909 – Expiry date NOV2011; Batch CTH0924 – Expiry date MAR2012 (Irbesartan 150 mg + hydrochlorothiazide 12.5 mg capsules); Batch CTD0923 – Expiry date DEC2011; Batch CTG0929 – Expiry date MAR2012 (Irbesartan 150 mg capsules).

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Criteria for evaluation (efficacy):

- Office diastolic blood pressure change at study end (24 weeks - baseline) (primary efficacy parameter);
- Office systolic blood pressure change at Visit 1 (8 weeks-baseline) and at study end (24 weeks - baseline);
- Office diastolic blood pressure change at Visit 1 (8 weeks-baseline);
- Rate of subjects with office blood pressure <140/90 mm Hg at Visit 1 (8 weeks) and at study end (24 weeks);
- Rate of subjects with office blood pressure <130/80 mm Hg at Visit 1 (8 weeks) and at study end (24 weeks);
- Rate of subjects with office blood pressure < 140/90 mm Hg or with an office systolic blood pressure reduction of at least 20 mm Hg or a diastolic blood pressure reduction of at least 10 mm Hg at Visit 1 (8 weeks) and at study end;
- 24 hour systolic and diastolic blood pressure changes at study end from baseline, only in a subgroup of patients;
- Day-time systolic and diastolic blood pressure changes at study end from baseline, only in a subgroup of patients;
- Night-time systolic and diastolic blood pressure changes at study end from baseline, only in a subgroup of patients;
- Rate of subjects with morning hypertension (ambulatory blood pressure in the morning, i.e. between 6:00 or waking time and 9:59, ≥ 135/85 mm Hg) at study end, only in a subgroup of patients;
- Last 6 hour systolic and diastolic blood pressure changes at study end from baseline, only in a subgroup of patients;
- Change in the morning surge at study end from baseline, only in a subgroup of patients;
- Rate of patients with morning surge above normal values (> 55 mm Hg) at study end, only in a subgroup of patients;
- Hourly systolic and diastolic blood pressure averages before and at the end of treatment, only in a subgroup of patients;
- Smoothness index of systolic and diastolic blood pressure at study end, only in a subgroup of patients;
- Change in AASI (Ambulatory Arterial Stiffness Index) at study end from baseline, only in a subgroup of patients;
- Change in fasting blood glucose (24 weeks – baseline);
- Change in HbA_{1C} (24 weeks – baseline);
- Change in plasma insulin (24 weeks – baseline);
- Change in HOMA-IR (Insulin –Resistance Index by Homeostasis Model Assessment) (24 weeks – baseline);
- Changes in creatinine clearance from baseline to the end of the double-blind period;
- Changes in urinary albumin-creatinine ratio from baseline to the end of the double-blind period;
- Change in serum triglycerides from the baseline to the end of the double-blind period;
- Change in HDL cholesterol from the baseline to the end of the double-blind period;
- Rate of patients with HbA_{1C} < 7% before and at the end of the double-blind period;
- Rate of patients with fasting blood glucose between 70 and 130 mg/dL before and at the end of the double-blind period;
- Rate of patients with reduced renal function (creatinine clearance < 60 ml/min) before and at the end of the double-blind period;
- Rate of patients with an albumin-creatinine ratio ≥ 22 mg/g if males or ≥ 31 mg/g if females before and at the end of the double-blind period;
- Rate of patients with microalbuminuria (urine albumin/creatinine ratio 30-300 mg/g) before and at the end of double-bind;
- Change in waist circumference from V0 (week 0) to the end of the double-blind period.

Criteria for evaluation (safety):

- The overall incidence of AEs;
- Evidence from physical examination;
- Vital signs (blood pressure and heart rate);
- ECG abnormalities;
- Laboratory parameters (haematology, blood chemistry, urinalysis).

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Statistical methods:
The statistical analysis had been performed using SAS® version 9.2. Descriptive statistics had to be provided for all variables in the summary tables by treatment group. Continuous variables had to be summarised by means of mean, standard deviation, median and range.

Categorical variables had to be summarised by using frequency distributions and percentages.

For the analysis within group, 95% CI for the mean changes from baseline had to be calculated.

For the primary efficacy variable, the bilateral confidence interval (1-2α) of the two means difference had to be calculated at α=0.025, therefore a 95% confidence interval had to be used.
For all the other variables, hypothesis testing had to be carried out at the α = 0.05 level (two-sided) when comparing treatments.

All p-values had to be rounded to three decimal places. Statistical significance had to be declared if the rounded p-value was less than or equal to 0.050.

The demographic and medical history data had to be summarized for the FAS population (and PP population if relevant) by means of descriptive statistics.

All efficacy analyses had to be carried out on the "full analysis set" (FAS) and “per-protocol” (PP) population. The FAS population had to include all randomised patients who have taken at least one dose of the study drug and have at least one office blood pressure determination during treatment. The PP population had to include all patients from the FAS population without any major protocol violation. For patients leaving the study prematurely the last available data post randomization had to be used for the final evaluation (24^{th} week) in accordance with the last observation carried forward (LOCF) method.

Evaluation of safety had to be performed on the “safety population”, i.e. on all randomized patients who have taken at least one dose of the active study drug.

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Results:

Analyses performed on baseline characteristics of the two treatment groups, revealed that subjects assigned to Zofenopril + HCTZ treatment were more compromised in terms of cardiovascular risk factors, evidencing statistically significant differences in the number of subjects with diabetes, and diabetic or under glucose lowering agents, and in the number of subjects dyslipidemic or under lipid modifying agents. Despite these differences, considering primary efficacy end-point (i.e. change, respect to baseline, in office sitting DBP after 24 weeks of treatment), results show a substantial equivalence between the two association (i.e. Zofenopril + HCTZ and Irbesartan + HCTZ), demonstrating, also from a statistical point of view, that the association of Zofenopril 30-60 mg + HCTZ 12.5 mg, given for 24 weeks to subjects affected by metabolic syndrome with essential hypertension not controlled by previous monotherapy, is at least as effective as the association of Irbesartan 150 to 300 mg + HCTZ 12.5 mg, in reducing the office sitting DBP. In fact, having fixed the non-inferiority margin at 2.5 mm Hg, the difference in adjusted mean changes of sitting office DBP, between baseline and the end of the study (i.e. after 24 weeks of treatment), in the two treatment groups, was -0.62 with the lower limit of the two-sided 95% CI for the difference equal to -1.970 (greater than the -2.5 mmHg).
The same result was confirmed by the analysis conducted on the PP population.

In 17 of the 21 considered secondary efficacy end-points no statistically significant differences between the two treatment groups were found.
Thus, only in few cases, the two groups differs in a statistically significant manner. In particular, the percentage of responder subjects (considering both those with an office sitting SBP reduction of at least 20 mmHg or a DBP reduction of at least 10 mmHg at visit 1 and at the study end and those with office blood pressure < 140/90 mm Hg or with an office SBP reduction of at least 20 mm Hg or a DBP reduction of at least 10 mm Hg at Visit 1 (8 weeks), and at study end) seems to be slightly higher, at visit 1 and only in the FAS population. Considering that this difference was no more observed at the end of the study, it can be concluded that despite its statistically significance, it doesn't have any clinical relevance.

As regards the change in albumin/ creatinine ratio (ACR) from baseline to study end, performed analyses showed a statistically significant difference between the two treatment groups, in particular, considering the FAS population, mean difference from baseline to study end in ACR was -29.9 mg/g in the Irbesartan + HCTZ group and -1.4 mg/g in the Zofenopril + HCTZ group. Similar results were obtained in the PP population.
Concerning the change in microalbuminuria from baseline to study end, the difference between the two treatment groups resulted statistically significant, and in the group of subjects treated with Irbesartan + HCTZ, and presenting microalbuminuria (i.e. ACR between 30 and 300 mg/g) at baseline, the decrease in mean value of ACR was greater than in the other group.
Despite results concerning ACR and albuminuria seems to be favorable to the combination Irbesartan + HCTZ, in the first case data could be deeply biased by the presence of an outlier in the comparator group while in the second one, number of subjects entered in the analysis of such end-point, is too little to allow reliable conclusions.
No other statistically and clinical significant differences between the two treatment groups were found in all other secondary end points considered.

Concerning ABPM, for all examined parameters, treatment with the Zofenopril + HCTZ combination provided a similar 24h BP control than Irbesartan + HCTZ.

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Results (cont.d):

With regard to safety, both the studied treatment and the comparator, resulted to be safe and well tolerated, showing a quite low rate of drug related adverse events. ADR were generally of mild or moderate intensity and only in one case, belonging to Irbesartan + HCTZ group, severe.
Adverse events were, in both treatment group, mainly related to nervous system (more frequently dizziness and headache) and to gastrointestinal disorders (more frequently diarrhoea, vomiting and nausea).
None of the occurred SAE were judged as treatment related.
Concerning other examined safety parameters (i.e. ECGs, vital signs and laboratory examinations), no other findings worthy of note were pointed-out.

Conclusions:
In conclusion, the results of the study indicate that administration of a combination therapy based on Zofenopril + HCTZ, combining different mechanisms of action, is at least efficacious as a combination of Irbesartan + HCTZ in controlling the office DBP of subjects with essential hypertension not controlled by a previous monotherapy and metabolic syndrome, while maintaining also a comparable safety profile. Moreover, the association under study demonstrated a comparable efficacy, respect to the comparator, in almost all secondary end points analysed, in particular on BP (i.e. DBP after 8 weeks of treatment, SBP at the different analysed time-points and percentage of responder subjects at the different time-points), ABPM and metabolic (e.g. fasting blood glucose, glycated haemoglobin, insulin resistance index, cholesterol, triglycerides), parameters.
Thus, the combination therapy based on Zofenopril + HCTZ, combining the anti-hypertensive activity with the antioxidative properties of Zofenopril, can be particularly indicated in the treatment of hypertensive subjects with other cardiovascular factors of risk.

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