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.

3 SYNOPSIS

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Title of the study:
A multicentre, multinational, randomised, double-blind, pilot, ascending dose for non-responder, parallel group study on the therapeutic efficacy and safety of o.d. Zofenopril 30 mg plus HCTZ 12.5 mg vs. Irbesartan 150 mg plus HCTZ 12.5 mg in elderly subjects (age > 65 years) affected by Isolated Systolic Hypertension never treated or non-responder to previous antihypertensive therapy (monotherapy or association of maximum two treatments).

Study Centres and Principal Investigator(s):

[redacted]

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Study Centres and Principal Investigator(s) (cont.d): [redacted]		
Publication (reference): na		
Studied period (years): **2010-2013**	**Date of first enrolment:** **29DEC10** **Date last visit completed:** **02MAY13**	**Phase of development:** **III, pilot**

Objectives:
To compare the antihypertensive efficacy of Zofenopril 30 mg plus HCTZ 12.5 mg versus Irbersartan 150 mg plus HCTZ 12.5 mg by assessment of the average reduction in mean day-time Systolic Blood Pressure (SBP) from baseline in the two groups after 6 weeks of treatment.

Methodology:
Multicentre, multinational, randomised, double-blind, pilot, phase III, ascending dose for non-responder, parallel group study.

Number of subjects (planned and analysed):
A total of 324 subjects were to be enrolled in the study to have at least 204 randomised subjects in two treatment groups. Subjects were to be enrolled in Italy, Romania, and Russia. A total of 24 clinical sites, 14 in Italy, 8 in Romania and 2 in Russia actively participated into the study. A total of 434 subjects were screened and 230 randomised (safety population). Out of them, 217 entered in the FAS population and thus in the efficacy statistical analyses.

Diagnosis and main criteria for inclusion and exclusion:
The study population included elderly subject suffering from Isolated Systolic Hypertension (ISH) with the following characteristics (inclusion criteria):

- Male or female subjects aged >65 years;
- Subjects willing and able to give written informed consent;
- Subjects having at baseline a sitting DBP < 90 mmHg and a sitting SBP ≥ 140 mmHg (value of office measurement) and a mean day-time DBP < 85 mmHg and a mean day-time SBP ≥ 135 mmHg (value of ambulatory blood pressure monitoring, i.e. ABPM);
- Previously untreated subjects or subjects who stopped their antihypertensive treatments since at least 6 months or subjects who were on treatment with mono- or combination therapies, of no more than two drugs that could not be Zofenopril, Irbesartan, Zofenopril associated with diuretics, Irbesartan associated with diuretics

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who satisfied the blood pressure level criteria for inclusion despite previous/concomitant treatment with another antihypertensive drug;

- Body mass index < 30 kg/m^2

Moreover, subjects had not to meet any of the following exclusion criteria:

- Subject with a sitting DBP ≥ 90 mmHg and/or a sitting SBP < 140 mmHg at baseline (value of office measurement);
- Subject with mean day-time DBP ≥ 85 mmHg and/or a mean day-time SBP < 135 mmHg;
- Subjects with a sitting SBP ≥ 200 mmHg at baseline;
- Subject with secondary or malignant hypertension;
- Myocardial infarction or cerebrovascular disorders within the last 6 months;
- Subjects who underwent coronary angioplasty within 6 months prior to enrolment in the study or subjects who underwent coronary angioplasty within 6 months after study entry;
- History or current evidence of severe heart failure (NYHA≥3);
- Haemodynamic relevant rhythm disturbances (including atrial flutter or atrial fibrillation with ventricular response, frequent ectopic beats, bradycardia (≤ 55 bpm), evidence of AV-block on ECG of more than 1st degree, serious arrhythmia);
- Arm circumference < 24 or > 32 cm;
- History of angioneurotic oedema;
- Clinically significant or unstable concurrent disease: uncontrolled diabetes, uncontrolled hypothyroidism, significant renal impairment (serum creatinine ≥ 2.0 mg/dL), significant hepatic impairment (AST or ALT twice the upper limit of the normal range), poorly controlled respiratory, gastro-intestinal, neurological or haematological disease, autoimmune disease, serum electrolytes disorders (e.g. hyperkalaemia);
- Subjects affected from neutropenia (WBC < 3,500/mm^3) and or anaemia (RBC < 3,500,000 mm^3);
- Participation in any investigational drug study in the 3 months before the start of the study;
- History of alcohol or drug abuse;
- Allergy, sensitivity or intolerance to study drugs and/or study drugs excipients;
- Previous antihypertensive treatments with Zofenopril, Irbesartan, Zofenopril associated with diuretics, Irbesartan associated with diuretics;
- Concomitant treatment, from V0 onwards, with other drugs that affect blood pressure (i.e. others ACE-inhibitors and/or diuretics, angiotensin II receptor antagonists, calcium antagonists, alfa- and beta-blockers, long-acting nitrates, MAO inhibitors, clonidine);
- Concomitant therapy with lithium, neuroleptics (i.e. haloperidol), indomethacin, NSAIDs, acetylsalicylic acid > 3 g/die, oral and parenteral corticoids, antiacid agents, potassium substitutes, class I and III antiarrhythmic agents, cardiac glycosides;
- Subjects unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study;
- Subjects who had been previously enrolled in this study.

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. 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, manufactured by A. Menarini MMLS – Firenze 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. Each dose consisted of two capsules, to be taken together.
- 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, Zofenopril 30 mg over-

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encapsulated in DBAA capsules suitable to keep the blinding manufactured by A. Menarini MMLS – Firenze, Nitrendipine 20 mg tablets. Each dose consisted of two capsules and one tablet, to be taken together.

Batch CTL1015 – Expiry date: AUG2013; batch CTD1219 - Expiry date: JAN2015 (Zofenopril 30 mg + hydrochlorothiazide 12.5 mg capsules); Batch CTM1015 – Expiry date SEP2013; batch CTD1217 – Expiry date JAN2015 (Zofenopril 30 mg capsules); Batch 02008 - Expiry date: MAY2013; batch 11004 – Expiry date: MAR2014 (Nitrendipine).

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. 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, manufactured by A. Menarini MMLS – Firenze, plus 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. Each dose consisted of two capsules, to be taken together.
- 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, plus Irbesartan 150 mg over-encapsulated in DBAA capsules suitable to keep the blinding manufactured by A. Menarini MMLS – Firenze, plus Nitrendipine 20 mg tablets. Each dose consisted of two capsules and one tablet, to be taken together.

Batch CTL1018 – Expiry date JUL2013; Batch CTD1212 – Expiry date JUL2014 (Irbesartan 150 mg + hydrochlorothiazide 12.5 mg capsules); Batch CTL1015 – Expiry date JUL2013; Batch CTD1210 – Expiry date OCT2014 (Irbesartan 150 mg capsules). Batch 02008 - Expiry date: MAY2013; batch 11004 – Expiry date: MAR2014 (Nitrendipine).

Criteria for evaluation (efficacy):

- <u>primary efficacy parameter</u>
  - Average reduction in mean day-time SBP from baseline to the end of the first step of treatment (6 weeks) in the two groups
- <u>secondary efficacy parameters</u>
  - 24-h Blood Pressure monitoring: average reduction in mean day-time SBP from baseline to the end of the second step (12 weeks) and third step of treatment (18 weeks) in the groups;
  - Day-time Normalisation rate (normalisation of mean day-time SBP < 135 mmHg and mean day-time DBP < 85 mmHg) at the end of first step (6 weeks), second step (12 weeks) and at the end of treatment (18 weeks);

Criteria for evaluation (efficacy) (cont.d):

- Office Normalisation rate (normalisation of office blood pressure to a sitting SBP < 140 mmHg and sitting DBP < 90 mmHg) at the end of first step (6 weeks), second step (12 weeks) and at the end of treatment (18 weeks);
- Day-time Responders rate (mean day-time SBP < 135 or reduction in mean day-time SBP from baseline ≥ 10 mmHg) at the end of first step (6 weeks), second step (12 weeks) and at the end of treatment (18 weeks);
- Office Responders rate (sitting office SBP < 140 or reduction in sitting office SBP from baseline ≥ 20 mmHg) at the end of first step (6 weeks), second step (12 weeks) and at the end of treatment (18 weeks);
- Mean change from baseline in office sitting and standing SBP and DBP at each visit (week 6, 12 and 18);

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- Changes in microalbuminuria and/or albumin-creatinine ratio before and/or after 18 weeks;
- Mean change from baseline in estimated creatinine clearance (mL/min, Cockroft-Gault formula) after 18 weeks of treatment
- Mean change from baseline at each visit (week 6, 12 and 18) for the cardiovascular risk score;
- Mean changes in indices of arterial stiffness (Pulse Wave Velocity or PWV and Augmentation Index or AI) and in central SBP after 6 weeks (end of the first step), after 12 weeks (end of the second step) and at the end of treatment (18 weeks)
- Rate of subjects with difference between SBP and DBP greater than 40 mmHg (Office SBP minus DBP > 40 mmHg) after 6 weeks (end of first step), after 12 weeks (end of the second step) and at the end of treatment (18 weeks).

Criteria for evaluation (safety):

- Overall incidence of AEs;
- Physical examination;
- Vital signs (including BP sitting and standing office measurement);
- ECG abnormalities;
- Laboratory safety parameters (haematology, blood chemistry, urinalysis).

Statistical methods:

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

Categorical variables were summarised by using frequency distributions and percentages.

For the analysis within group, the 95% confidence interval (CI) for the mean changes from baseline was calculated.

For the primary efficacy variable, the bilateral CI (1-2α) of the two difference between the two means was calculated at α=0.025, therefore a 95% CI was used.

For all the other variables, hypothesis testing was carried out at the $\alpha = 0.05$ level (two-sided) when comparing treatments.

All p-values were rounded to three decimal places. Statistical significance was declared if the rounded p-value was less than or equal to 0.050.
All efficacy analyses were carried out on the "full analysis set" (FAS) and in the "per-protocol" (PP) population. The FAS population included all randomised patients who took at least one dose of the study drug and had at least one reliable post baseline ABPM assessment during treatment. The PP population included all patients from the FAS population without any major protocol violation. For patients leaving the study prematurely, the last available data post randomization was used for the final evaluation (18^{th} week) in accordance with the last observation carried forward (LOCF) method. Moreover, all efficacy analyses were carried out on all other identified subgroups according to the Statistical analysis plan agreed with the Sponsor after the protocol finalisation.

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

Evaluation of safety was performed on the "safety population", i.e. on all randomized patients who took at least one dose of the active study drug.

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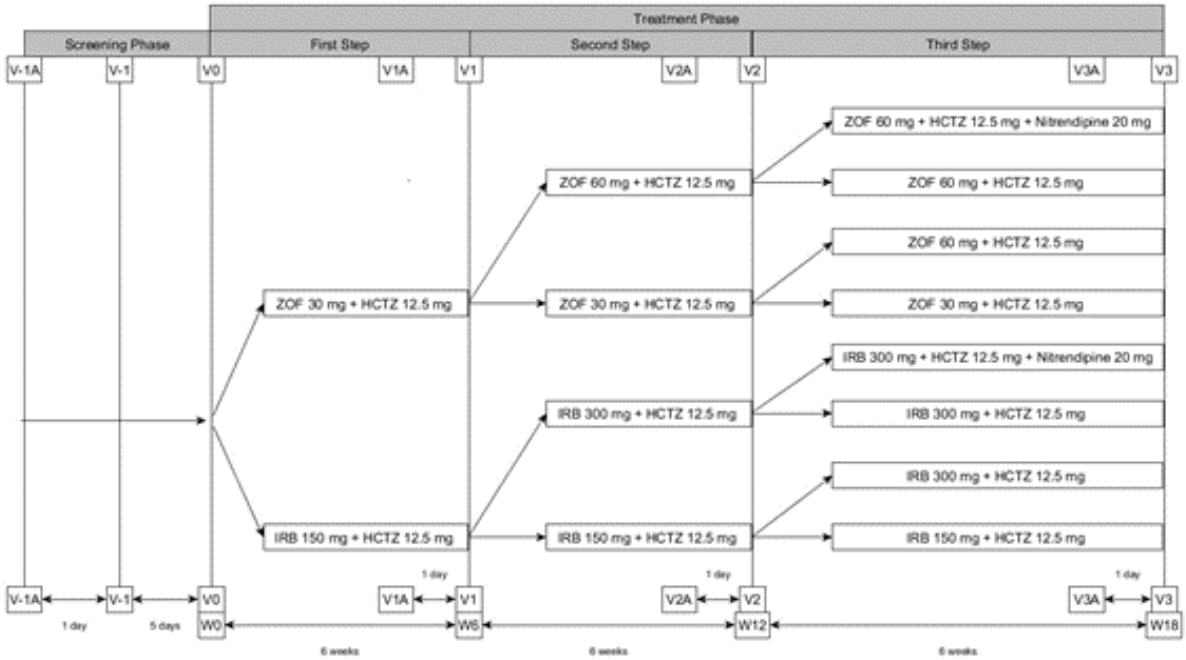
Study design, schedule of assessment and subjects disposition:



Eligible subjects were randomised to an 18 weeks treatment period. The treatment period consisted of 3 steps at week 6, 12 and 18. After 6 weeks of treatment (first step), subjects who were non responder (sitting DBP < 90 and sitting SBP ≥ 140 mmHg plus mean day-time DBP < 85 mmHg and mean day-time SBP ≥ 135 mmHg), considering ABPM and sitting office blood pressure, were uptitrated to Zofenopril 60 mg plus HCTZ 12.5 mg (o.d.) or Irbersartan 300 mg plus HCTZ 12.5 mg (o.d.) until week 12. After 12 weeks from randomisation (second step), subjects already uptitrated at step 1 who were non responder received Nitrendipine 20 mg in addition to the study treatment or, if they were responders at step 1 but non responder at step 2, were uptitrated to Zofenopril 60 mg plus HCTZ 12.5 mg (o.d.) or Irbersartan 300 mg plus HCTZ 12.5 mg (o.d.) until week 18. Responder subjects during step 2 and 3 continued without changes in the study treatments up to week 18. Possible treatments in the 3 phases are showed in the above scheme, while number of subjects (belonging to the FAS population) entered in the different steps of the study are reported in the table below.

FAS population at different study steps						
	ZOF 30 +HCTZ	**ZOF 60+HCTZ**	**Irbe 150+HCTZ**	**Irbe 300+HCTZ**	**ZOF 60 + HCTZ+nitrend**	**Irbe 300 + HCTZ+nitrend**
1st step (V0-V1)	**107**	**na**	**109**	**na**	**na**	**na**
2nd step (V1-V2)	**49 (46%)**	**58 (54%)**	**54 (50%)**	**55 (50%)**	**na**	**na**
3rd step (V2-V3)	**36 (34%)**	**36 (34%)**	**41 (38%)**	**41 (38%)**	**35 (33%)**	**27 (25%)**

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Results:

Baseline characteristics of the two treatment groups were overall similar, with the only exception of presence of metabolic syndrome that was significantly different in the two groups (p = 0.007 and p = 0.021 in Safety and FAS populations, respectively) being worst in the Zofenopril + HCTZ group. Considering the primary efficacy end-point (i.e. mean change, respect to baseline, in average day-time SBP after 6 weeks of treatment to subjects affected by ISH not controlled by previous monotherapy or by the combination of a maximum of two treatments), the combination of Zofenopril 30 mg + HCTZ 12.5 mg was as effective as the association of Irbesartan 150 mg + HCTZ 12.5 mg (p= 0.969, not statistically significant). In fact, having set a possible difference of 8 mm Hg between groups, the difference in adjusted mean changes of mean day-time SBP, between baseline and visit 1 (i.e. after 6 weeks of treatment), in the two treatment groups, was -0.21 being the lower and upper limits of the two-sided 95% CI for the difference equal to -3.066 and 2.655 respectively (within the 8 mmHg difference).
Similar esults were obtained in the PP population and in all the other analyzed FAS subgroups.

Considering the 107 and 109 subjects, respectively in the Zofenopril 30 mg+HCTZ group and in the Irbesartan 150 mg + HCTZ group, entered in the FAS population at V0 (first step of the study), 49 (46%) in the Zofenopril 30 mg + HCTZ group and 54 (50%) in the Irbesartan 150 mg + HCTZ group reached the BP target after 6 weeks of treatment (end of the first step), while 58 subjects (54%) in the Zofenopril +HCTZ group and 55 (50%) in the Irbesartan +HCTZ group had the dose escalated to the higher one. At the end of the second step, half (29/58) of the subjects receiving Zofenopril 60 mg + HCTZ had a normalized BP. At the end of the study (V3, after 18 weeks of treatment) 66.7% of the subjects having taken the higher dosage of Zofenopril were normalized.
As far as concern the secondary efficacy end-points and all analyzed FAS subpopulations, results obtained in the two treatment groups showed in most cases a similar efficacy, with the exception of few cases in which the two groups differed in a statistically significant extent.
In particular, in the FAS population for the day time normalization rate, the percentage of subjects with normalized day-time blood pressure at visit 3 (after 18 weeks) was significantly higher in the Zofenopril + HCTZ group than in the Irbesartan + HCTZ group (p = 0.031). This result was confirmed also in the PP, FAS Italian, FAS low dose, and FAS sustained hypertension populations.
Similarly, in the day-time responder rate, the percentage of responder subjects (mean day-time SBP<135 mmHg or reduction ≥ 10 mmHg with respect to baseline) at visit 3 (week 18) was higher in the Zofenopril + HCTZ group than in the Irbesartan + HCTZ group in the FAS (p = 0.049 between groups), PP, FAS Italian and FAS low dose populations.
In the FAS low dose population, the combination Zofenopril 30 mg + HCTZ 12.5 mg was significantly superior to Irbesartan 150 mg + HCTZ 12.5 mg in reducing the mean day-time from baseline to study end (p=0.028).
Finally the results of arterial stiffness indexes, involved in the ISH pathogenesis, showed that the efficacy of the two treatments was similar without any statistically significant difference.

With regard to safety, both study combinations resulted to be safe and well tolerated. All ADR were of mild or moderate intensity, most of them in the Irbesartan + HCTZ group (15 vs 9).
Adverse events (105 in the Irbesartan + HCTZ group vs 61 in the Zofenopril + HCTZ group) were, in both treatment groups, mainly related to gastrointestinal system (more frequently diarrhoea and upper abdominal pain) and to general disorders and administration site conditions (more pyrexia).

Neither the occurred SAEs nor the sudden death occurred in the Irbesartan + HCTZ group, 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, apart from the only clinically relevant abnormality in the ECG (first degree AV block) at the final examination occurred to one subject in the Irbesartan + HCTZ group.

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Conclusions:

The results of the study indicate that the administration of a combination therapy based on Zofenopril + HCTZ was as effective as a combination of Irbesartan + HCTZ in controlling the mean day time SBP of subjects with essential ISH (not controlled by a previous monotherapy or a combination therapy of a maximum two treatments), showing in the same time a similar safety profile.

Moreover, the associations under study demonstrated a comparable efficacy in almost all secondary end points analysed, both in all those relevant to Blood Pressure control and those relevant to renal function. These latter results deserve more consideration as Irbesartan showed in previous studies to be very effective in improving renal function.

In conclusion, the combination therapy based on Zofenopril + HCTZ, can be considered a therapeutical option for those subjects affected by ISH not controlled by a previous monotherapy or by a combination of a maximum two treatments. Moreover, the results obtained with the higher dose of the test treatment suggest that Zofenopril 60 mg + HCTZ can be of benefit in most of subjects not responding to the lower dosage, wgile maintaining the same safety profile.

Date of the report: Final version, 18/03/2015