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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

Title of the Study:
Efficacy and safety of zofenopril + hydrochlorothiazide combination vs. irbesartan + hydrochlorothiazide combination in essential hypertensive patients not controlled by previous monotherapy.
Double blind, multicentre, phase III study in essential hypertensive patients.

Protocol number: MeIn/08/ZOF+HCTZ-HYP/001. EudraCT number 2008-002439-33

Investigator(s):
Coordinating Investigators [redacted]

Study Center(s):
28 centres in 5 countries: Italy (7 centres), Greece (3 centres), Lithuania (3 centres), Romania (5 centres) and Turkey (10 centres).
Actively including patients:
27 centres in 5 countries: Italy (7 centres), Greece (3 centres), Lithuania (3 centres), Romania (4 centres) and Turkey (10 centres).

Studied Period:	First patient enrolled: 17.11.2008 Last patient completed: 06.07.2010	**Clinical Phase:**	III

Objective(s):
Primary:
The primary study objective is to determine whether the combination zofenopril + hydrochlorothiazide is at least as effective as the irbesartan + hydrochlorothiazide combination in reducing office sitting diastolic blood pressure after 18 weeks of treatment in essential hypertensive patients not controlled by a previous monotherapy and with one or more additional cardiovascular risk factors.

Secondary:
The assessment of efficacy on office sitting systolic blood pressure, on ambulatory blood pressure and on a marker of cardiovascular organ damage such as hs-CRP (high sensitivity C Reactive Protein – only selected sites).

Methodology: non-inferiority trial with a randomized, double-blind, parallel group, controlled design. Following a run-in period of 2 weeks of single-blind placebo treatment, patients were randomized to receive in double-blind conditions either zofenopril, 30 mg + hydrochlorothiazide 12.5 mg, or irbesartan, 150 mg + hydrochlorothiazide 12.5 mg, for 18 weeks. After 6 or 12 weeks of treatment patients not controlled (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg or SBP $\geq$ 130 mmHg or DBP $\geq$ 80 mmHg in case of diabetics or high risk patients) were up-titrated to zofenopril 60 mg + hydrochlorothiazide 12.5 mg or irbesartan 300 mg + hydrochlorothiazide 12.5 mg. Thereafter patients who received up-titration entered a 14-weeks extension period.

Number of Subjects:

- Planned: 320 randomised patients
- Screened: 408 patients
- Randomized: 361 patients (180 to zofenopril + hydrochlorothiazide and 181 to irbesartan + hydrochlorothiazide).
- Completed treatment phase: 353 patients (ITT/FAS: zofenopril + hydrochlorothiazide 175 and irbesartan + hydrochlorothiazide 178).
- Completed treatment phase: 294 patients (PPS: zofenopril + hydrochlorothiazide 152 and irbesartan + hydrochlorothiazide 142).
- Completed treatment phase: 235 patients (ABPM-PP: zofenopril + hydrochlorothiazide 119 and irbesartan + hydrochlorothiazide 116).

Analyzed

- Safety: 361 patients (zofenopril + hydrochlorothiazide 180 and irbesartan + hydrochlorothiazide 181).
- Efficacy (FAS): 353 patients (zofenopril + hydrochlorothiazide 175 and irbesartan + hydrochlorothiazide 178).
- Efficacy (PPS): 294 patients (zofenopril + hydrochlorothiazide 152 and irbesartan + hydrochlorothiazide 142).
- Efficacy (ABPM-PP): 235 patients (zofenopril + hydrochlorothiazide 119 and irbesartan + hydrochlorothiazide 116).

Diagnosis and Criteria for Inclusion:
Patients meeting the following criteria were included:

- Outpatients aged 18-75 years
- Male and female gender (females of childbearing potential must be using adequate contraceptive precautions such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence or vasectomised partner)
- Females of childbearing potential or within two years from the menopause must have a negative urine pregnancy test
- Patients with essential hypertension currently taking one antihypertensive medication (ACE-inhibitor, AT1-antagonist, diuretic, calcium antagonist, beta-blocker) and not adequately controlled (office DBP $\geq$ 90 mm Hg)
- One or more additional cardiovascular risk factors among:
  - Smoking
  - Total cholesterol >5.0 mmol/l (190 mg/dL) or on specific drug treatment
  - LDL cholesterol >3.0 mmol/l (115 mg/dL) or on specific drug treatment
  - HDL cholesterol <1.0 mmol/l (40 mg/dL) in males; <1.2 mmol/ (46 mg/dL) in females, or on specific drug treatment
  - Diabetes mellitus controlled by diet or antidiabetic treatment (HbA1c $\leq$ 7.5%)
  - Abdominal obesity: waist circumference >102 cm in males; >88 cm females or BMI $\geq$25 and $\leq$ 32 kg/m^2
  - Family history of premature cardiovascular disease (males at age <55 years; females at age <65 years)
- Able and willing to sign informed consent and to comply with study procedures
- Written informed consent of the patient

Test Product, Dose, Mode of Administration, Batch No(s):
Zofenopril 30 mg + hydrochlorothizide 12,5 mg encapsulated fixed dose coated tablets once a day by oral route
Batch N: CTI0811; CTM0805
Zofenopril 30 mg encapsulated coated tablets once a day by oral route
Batch N: CTI0805; CTA0915

Reference Therapy, Dose, Mode of Administration, Batch No(s):
Irbesartan 150 mg + hydrochlorothizide,12,5 mg encapsulated fixed dose tablets once a day by oral route
Batch N: CTH0807; CTM0811
Irbesartan 150 mg encapsulated coated tablets once a day by oral route
Batch N: CTH0829; CTL0827

Duration of Treatment:
For the individual patient:

- **Double blind period:**
  Run-in: 2 weeks Treatment (until visit 3b): 18 weeks (Total: 20 weeks).
- **Extension period:**
  Treatment (from V3b until visit 5): additional 14 weeks.
- **Total treatment period Double blind +Extension period:**
  34 weeks including run-in period.

Global study duration:
Total recruitment period (first patient in to last patient in): 62 weeks
Study conduct (last patient in to last patient completed until Visit 3b): 85 weeks

Criteria for Evaluation:
Main efficacy criteria

Primary efficacy variable:
Office sitting diastolic blood pressure change after 18 weeks of treatment (Visit 3b – baseline)

Secondary variables:
- Office sitting systolic blood pressure change after 18 weeks of treatment (Visit 3b – baseline)
- Percentage of subjects with sitting office blood pressure <140/90 mmHg after 18 weeks of treatment
- Percentage of subjects with sitting office blood pressure <130/80 mmHg after 18 weeks of treatment
- Percentage of subjects with sitting office blood pressure <140/90 mmHg or with an office sitting systolic blood pressure reduction of at least 20 mmHg or a sitting diastolic blood pressure reduction of at least 10 mmHg after 18 weeks of treatment
- 24 hour systolic and diastolic blood pressure changes after 18 weeks of treatment from baseline
- Day-time systolic and diastolic blood pressure changes after 18 weeks of treatment from baseline
- Night-time systolic and diastolic blood pressure changes after 18 weeks of treatment from baseline
- 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 mmHg) after 18 weeks of treatment
- Last 6 hour systolic and diastolic blood pressure changes after 18 weeks of treatment from baseline
- Change in the morning surge after 18 weeks of treatment from baseline
- Rate of patients with morning surge above normal values (>55 mmHg) after 18 weeks of treatment (Visit 3b – baseline)
- Hourly systolic and diastolic blood pressure averages before and after 18 weeks of treatment
- Smoothness index of systolic and diastolic blood pressure after 18 weeks of treatment
- Change in AASI after 18 weeks of treatment from baseline
- Change in hs-CRP from baseline

Safety criteria
Overall incidence of adverse events (AEs)
- Evidence from physical examination
- Heart rate
- Standing blood pressure
- ECG abnormalities
- Laboratory parameters (haematology, blood chemistry, urinalysis)

Statistical Methods:
Primary parameter was the office sitting diastolic blood pressure (DBP) change from baseline to the end of double-blind period (18 weeks – baseline).
Comparison between the two groups for the primary efficacy parameter was to be carried out by covariance analysis (ANCOVA). The analytical model had to include the treatment factor and the baseline value as covariate; centre effect was to be included in the main model. The Last Observations Carried Forward (LOCF) method was used to replace missing data for any cause; the 95% confidence intervals (CI) for the estimate of the difference (zofenopril + HCTZ) - (irbesartan + HCTZ) was to be provided and the upper bound compared with the 3 mmHg non-inferiority limit.
Considering that the country effect was found significant, its interaction with treatment was investigated in a further analysis. Both the FAS and the PPS were to be considered as the confirmatory sets.
The same model was to be used for the analysis of the secondary parameter: office sitting Systolic Blood Pressure (STB) change after 18 weeks of treatment. Percentage of subjects with sitting office blood pressure <140/90 mmHg after 18 weeks of treatment, percentage of subjects with sitting office blood pressure <130/80 mmHg after 18 weeks of treatment and percentage of subjects with sitting office blood pressure <140/90 mmHg or with an office sitting systolic blood pressure reduction of at least 20 mmHg or a sitting diastolic blood pressure reduction of at least 10 mmHg after 18 weeks of treatment were to be analyzed by the Fisher exact tests and the 95% CI of the asymptotic difference in proportion provided.
The minimum level of statistical significance was set at 2.5% (one sided) for non-inferiority testing and 5% (two-sided) otherwise.

RESULTS:

Baseline characteristics

The patient population recruited in this study consisted in patients of both sexes, with a prevalence of males (63.9%) and with a broad range of ages (18-76 years) with higher median age in the zofenopril + hydrochlorothiazide group (57.0 years versus 53.0 years). On average the patients were overweight with a median BMI of 28.0 in both treatment groups. Most of them were high risk patients 93.4% (92.2% in the ZOF+HCTZ group and 94.5% in the IRB+HCTZ group); 83.4% had at least one concomitant disease (85.0% in the ZOF+HCTZ group and 81.8% in the IRB+HCTZ group) and 50.4% was taking at least one concomitant medication (56.7% in the ZOF+HCTZ group and 44.2% in the IRB+HCTZ group).

In the FAS population there were significant differences between the characteristics of the two treatment groups at entry for:

- age, which in the ZOF+HCTZ group was higher (56.4±10.6) than in the IRB+HCTZ group (53.9±10.6) (p=0.024);
- waist circumference, which in the ZOF+HCTZ group was higher (99.9±9.8) than in the IRB+HCTZ group (97.4±10.4) (p=0.023);
- cardiovascular Risk Factors, which in the ZOF+HCTZ group was higher than in the IRB+HCTZ group (p=0.039).

  The Cardiovascular Risk Factor is a dichotomous index that assumes the value "1" if one, or more, of the followings conditions are present:
  1. age (>= 63.3 years, third percentiles);
  2. waist circumference (>= 106 cm, third percentiles);
  3. smoking history (currently smokers);
  4. alcool (average consumption);
  5. diabetes (diagnosis of diabetes at baseline visit).

  The Cardiovascular Risk Factor assumes the value "0" if any condition is present.

In the PP population there were significant differences between the characteristics of the two treatment groups at entry for:

- waist circumference, which in the ZOF+HCTZ group was higher (100.6±9.5) than in the IRB+HCTZ group (97.4±10.1) (p=0.005);
- smoking history, the percentage of "currently smokers" in the ZOF+HCTZ group was higher (66.4±33.6) than in the IRB+HCTZ group (76.8±23.2) (p=0.050);
- cardiovascular Risk Factor, which in the ZOF+HCTZ group was higher than in the IRB+HCTZ group (p=0.008).

In the ABPM-PP population there were significant differences between the characteristics of the two treatment groups at entry for:

- waist circumference, which in the ZOF+HCTZ group was higher (100.5±9.7) than in the IRB+HCTZ group (97.7±10.6) (p=0.038);
- cardiovascular Risk Factor, which in the ZOF+HCTZ group was higher than in the IRB+HCTZ group (p=0.014).

The proportion of patients suffering from at least one concomitant disease was similar in the two treatment groups: in the ZOF+HCTZ group 153/180 patients (85%) vs 148/181 patients (82%) in the IRB+HCTZ group. The most common concomitant diseases were: metabolism and nutrition disorders (69%), cardiac disorders (9%), gastrointestinal disorders (8%) and reproductive system and breast disorders (9%).

The proportion of patients who were taking concomitant medications was higher in the zofenopril + hydrochlorothiazide treatment group: 102/180 patients (57%) vs 79/181 patients (44%) in the irbesartan + hydrochlorothiazide group. The most common concomitant medications were cholesterol and triglyceride reducers (25%), antithrombotic agents (16%), and oral blood glucose lowering drugs (11%).

All patients, except one in the ZOF+HCTZ group were already on antihypertensive treatment and the most commonly used antihypertensive treatments were the same in the two treatment groups: ACE inhibitor monotherapy, angiotensin II antagonist monotherapy and some other.

Efficacy

Primary endpoint

- In the FAS population DBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -17.6 mmHg and -15.0 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the FAS [p=0.134] even if the trend of reduction was in favour of zofenopril + HCTZ 14.8% > than reduction induced by irbesartan + HCTZ.
  In the FAS population time course of DBP changes was similar until V1, at V2 and at V3 the effect of Irbesartan + HCTZ was slithery reduced, while the effect of Zofenopril + HCTZ remains consistent and permanent within the time. Both treatments reduced significantly DBP at V3 versus baseline.
- In PPS population DBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -12.4 mmHg and -13.3 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the PPS [p=0.666].
- In ITT population DBP change at V3 vs. Baseline, adjusted for the covariate risk factor, was -15.01 mmHg and -14.28 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the ITT [p=0.690].
- In ITT, sub-set population 24h/office BP-ABPM, DBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -14.93 mmHg and -11.27 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the ITT sub set [p=0.092] even if the trend of reduction was in favour of zofenopril + HCTZ 24.5% > than reduction induced by irbesartan + HCTZ.
  In ITT, sub-set population 24h/office BP-ABPM, time course of DBP changes was similar until V1, at V2 and at V3 the effect of Irbesartan + HCTZ was reduced, while the effect of Zofenopril + HCTZ remains consistent and permanent within the time. Both treatments reduced significantly DBP at V3 versus baseline.
- In sub-group A ABPM, DBP change at V3 vs. Baseline was -16.0 mmHg and -15.9 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the sub-group A ABPM [p=0.305].
- In sub-group B ABPM, DBP change at V3 vs. Baseline was -16.5 mmHg and -16.9 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the sub-group B ABPM [p=0.397].
- In sub-set population#1 high dose, zofenopril 60 mg + HCTZ 12.5 mg or irbesartan 300 mg + HCTZ 12.5 mg, DBP change at V3 vs. Baseline was -12.11 mmHg and -11.64 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the sub-set population #1 [p=0.800].
- In sub-set population#2 normal dose, zofenopril 30 mg + HCTZ 12.5 mg or irbesartan 150 mg + HCTZ 12.5 mg, DBP change at V3 vs. Baseline was -19.8 mmHg and -14.5mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as not reached in the sub-set population #2 where Zofenopril + HCTZ group was statistically significantly higher [p=0.022] than Irbesartan + HCTZ one in reducing DBP versus baseline and the reduction induced by zofenopril + HCTZ administration was 27.0% > than reduction induced by irbesartan + HCTZ.
- In mild hypertension sub-population, DBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -14.5 mmHg and -14.3 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the mild hypertension sub-population [p=0.902].
- In moderate hypertension sub-population, DBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -20.05 mmHg and -14.7 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as not reached in the moderate hypertension sub-population where Zofenopril + HCTZ group was statistically significantly higher [p=0.035] than Irbesartan + HCTZ one in reducing DBP versus baseline and the reduction induced by zofenopril + HCTZ administration was 26.5% > than reduction induced by irbesartan + HCTZ.
- In diabetic patients sub-population, DBP change at V3 vs. Baseline was -16.5 mmHg and -15.0 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. Non-inferiority criteria can be considered as reached in the mild hypertension sub-population [p=0.366].

Secondary endpoints double-blind period:

- **Office sitting SBP change at the end of double-blind period**
  SBP decreases significantly in both groups ($p < 0.001$).
  - In the FAS population SBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -21.5 mmHg and -20.6 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.691].
    In the FAS population time course of SBP changes was similar until V3 for both treatments.
  - In PPS population SBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -

18.8 mmHg and -18.8 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.993].

- In ITT population SBP change at V3 vs. Baseline was -22.8 mmHg and -19.6 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.740].
- In ITT, sub-set population 24h/office BP-ABPM, SBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -22.15 mmHg and -15.77 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. A statistical difference was observed between groups [p=0.034] in favour of zofenopril + HCTZ.
  In ITT, sub-set population 24h/office BP-ABPM, time course of SBP changes was similar until V1, at V2 and at V3 the effect of Irbesartan + HCTZ was reduced, while the effect of Zofenopril + HCTZ remain consistent and permanent within the time. Both treatments reduced significantly SBP at V3 versus baseline; difference between the 2 treatment is statistically significant [p=0.034].
- In sub-group A ABPM, SBP change at V3 vs. Baseline was -19.6 mmHg and -21.5 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.101].
- In sub-group B ABPM, SBP change at V3 vs. Baseline was -20.3 mmHg and -22.5 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.458].
- In sub-set population#1 high dose, zofenopril 60 mg + HCTZ 12.5 mg or irbesartan 300 mg + HCTZ 12.5 mg, SBP change at V3 vs. Baseline was -18.9 mmHg and -17.0 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups in the sub-set population #1 [p=0.503].
- In sub-set population#2 normal dose, zofenopril 30 mg + HCTZ 12.5 mg or irbesartan 150 mg + HCTZ 12.5 mg, SBP change at V3 vs. Baseline was -25.8 mmHg and -22.0 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups in the sub-set population #2 [p=0.274].
- In mild hypertension sub-population, SBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -15.88 mmHg and -15.73 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.959].
- In moderate hypertension sub-population, SBP change at V3 vs. Baseline, adjusted for the covariates risk factor and country, was -31.8 mmHg and -28.5 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.402].
- In diabetic patients sub-population, SBP change at V3 vs. Baseline was -18.0 mmHg and -22.2 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.155] even if the trend of SBP reduction was in favour of irbesartan + HCTZ 20.8% > than reduction induced by zofenopril + HCTZ.

- **Percentage of Subjects with Office sitting blood pressure <140/90**
  - In the FAS population percentage of responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 79.6% and 79.5% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.973].
  - In the PPS population percentage of responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 72.1% and 72.2% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.981].
  - In sub-set population #1 percentage of responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 62.2% and 64.6% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.751].
  - In sub-set population #2 percentage of responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 90.9% and 88.2% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.672].
- **Percentage of Subjects with Office sitting blood pressure <130/80**
  - In the FAS population percentage of responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 59.3% and 53.6% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.387]; the trend was in favour of zofenopril + HCTZ treatment.
  - In the PPS population percentage of responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 49.5% and 41.1% respectively in zofenopril + HCTZ treated patients and in irbesartan +

HCTZ treated one. No statistical difference was observed between groups [p=0.232]; the trend was in favour of zofenopril + HCTZ treatment.

- In sub-set population #1 percentage of responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 45.9% and 38.4% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.340]; trend was in favour of zofenopril + HCTZ.

- In sub-set population #2 percentage of responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 68.2% and 64.7% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.721].

- **Percentage of subjects with sitting office blood pressure <140/90 mmHg or with an office sitting systolic blood pressure reduction of at least 20 mmHg**

  - In the FAS population percentage of normalized+responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 88.4% and 88.5% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.981]; the trend was in favour of zofenopril + HCTZ treatment.

  - In the PPS population percentage of normalized+responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 72.1% and 72.2% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.981]; the trend was in favour of zofenopril + HCTZ treatment.

  - In the ITT population percentage of normalized+responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 93.4% and 85.6% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.081]; trend of normalization was in favour of zofenopril + HCTZ treatment.

- **Percentage of subjects with sitting office blood pressure <130/80 mmHg or with an office sitting systolic blood pressure reduction of at least 20 mmHg**

  - In the ITT population percentage of normalized+responders at V3 vs. Baseline, adjusted for the covariates risk factor and country, was 84.6% and 71.1% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. A statistical difference was observed between groups [p=0.027]; trend of normalization was in favour of zofenopril + HCTZ treatment.

- **24 hour systolic and diastolic blood pressure changes after 18 weeks of treatment from baseline**

  - Average SBP and DBP hourly values were similarly and consistently reduced by both treatments regimes in the ITT set and in PPS and by both dose level used. A similar trend was also observed when changes were evaluated in subgroups A and B (ITT). No statistical difference was observed between groups.

- **Change in the morning surge after 18 weeks of treatment from baseline**

  - The magnitude and the prevalence of morning surge were slightly reduced or not modified by 18 weeks of Zofenopril + HCTZ administration while the magnitude and the prevalence of morning surge were slightly increased by 18 weeks of Irbesartan + HCTZ administration. Development of abnormal morning surge during treatment was 19% and 24% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.074]; the trend was in favour of zofenopril + HCTZ treatment.

- **Last 6 hour systolic and diastolic blood pressure changes after 18 weeks of treatment from baseline**

  - Baseline adjusted changes for last 6h SBP and DBP hourly values were consistently reduced by both treatments in the ABPM-ITT set in both subgroups A and B. No statistical difference was observed between groups, the trend of reduction was in favour of Irbesartan + HCTZ

- **Hourly systolic and diastolic blood pressure averages before and after 18 weeks of treatment**

  - Average hourly DBP and SBP variation, before and after 18 weeks of treatment, detected at baseline and at V3b, was comparable for the two study drugs considering both SBP and DBP parameters.

- **Smoothness index of systolic and diastolic blood pressure after 18 weeks of treatment**

  - SIs values ameliorate after 18 weeks of treatments with study treatments. In both SBP and DBP, SIs amelioration did not differ between treatment groups in ITT population, normal and high dose groups, and in PPS population, normal and high dose groups, and in sub groups A and B. No statistical difference was observed between groups as well as no difference in amelioration trend.

- **Change in AASI after 18 weeks of treatment from baseline**

  - AASI was similarly and slightly reduced by both treatments by 6.4% and 4.2% respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups; the trend was in favour of zofenopril + HCTZ treatment. Considering the absolute rete of reduction, Zofenopril + HCTZ treatment was 37.5% more effective than Irbesartan + HCTZ treatment in reducing AASI

values.

- **Change in hs-CRP from baseline**
  - At the end of the 18 weeks treatment period, hs-CRP showed a decrease in the zofenopril + hydrochlorothiazide group -0.52, while in the irbesartan + hydrochlorothiazide showed an increase +0.97; the difference found between treatments is statistically significant p=0.001.

Secondary endpoints Extension Phase:

- **Office sitting diastolic blood pressure change after 32 weeks of treatment**
  - In the EXT population all treated patients show a significant and consistent decrease in sitting DBP. Change of DBP at V5 vs. Baseline, adjusted for the covariates risk factor and country, was -15.76 mmHg and -11.72 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.072], even if the trend of DBP reduction was in favour of zofenopril + HCTZ 25.6% > than reduction induced by irbesartan + HCTZ.
- **Office sitting systolic blood pressure change after 32 weeks of treatment**
  - In the EXT population all treated patients show a significant and consistent decrease in sitting SBP. Change of SBP at V5 vs. Baseline, adjusted for the covariates risk factor and country, was -23.07 mmHg and -19.84 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.296], even if the trend of DBP reduction was in favour of zofenopril + HCTZ 14.0% > than reduction induced by irbesartan + HCTZ.
- **Percentage of Subjects Normalized (sitting office BP <140/90 mmHg) + Responder (office sitting SBP reduction > 20mmHg or DBP reduction > 10 mmHg) after 32 weeks**
  - The percentage of Normalized+Responders, evaluated considering the EXT population, indicate that zofenopril + HCTZ and ibersantan + HCTZ treated patients, after 32 weeks of administration, had a similar response in blood pressure reduction.
    Percentage of normalized+responders was -89.4 mmHg and -87.00 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.589].
- **Percentage of Subjects Normalized (sitting office BP <130/80 mmHg) + Responder (office sitting SBP reduction > 20mmHg or DBP reduction > 10 mmHg) after 32 weeks**
  - The percentage of Normalized+Responders, evaluated considering the EXT population, indicate that zofenopril + HCTZ and ibersantan + HCTZ treated patients, after 32 weeks of administration, had a similar response in blood pressure reduction.
    Percentage of normalized+responders was -80.5 mmHg and -78.7 mmHg respectively in zofenopril + HCTZ treated patients and in irbesartan + HCTZ treated one. No statistical difference was observed between groups [p=0.736].

SAFETY

The safety data collected in this study show that both combination drugs are well tolerated in hypertensive patients treated for a 32 weeks period. Three hundreds and sixty-one (361) patients were included in the Safety Set: 180 and 181 of which received zofenopril + HCTZ and irbesartan + HCTZ respectively.
A total 125 patients, 71 (39.4%) in the zofenopril + HCTZ group and of 54 patients (28.8%) in the irbesartan + HCTZ group, reported at least one treatment-emergent adverse event with any relation to study medication.The number of patients who reported at least one related treatment-emergent adverse event was inferior to 12% in both groups.

A total of 35 patients, 21 (11.6%) in the zofenopril + HCTZ group and 14 patients (7.7%) in the irbesartan + HCTZ group, reported at least one adverse event related to study medication (i.e. classified by the investigator as certainly, probably or possibly related).

A total of 9 Serious Adverse Events were recorded in 7 patients. Six patients (3.3%%) in the zofenopril + HCTZ group reported at least one serious adverse event (SAE) during the study period baseline-V5; and 1(0.55%) patient reported 2 SAE in the irbesartan + HCTZ group during the same study period. No one of the 7 events recorded in the zofenopril + HCTZ was considered by the investigator as related to study treatment with the exception of a myocardial infarction considered not related by the investigator but upgraded to possibly related by the Sponsor; one of the 2 events recorded in the irbesartan + HCTZ group, hyperglycemia, was considered not related by the investigator but upgraded to possibly related by the Sponsor.

Nine patients (5%) in the zofenopril + HCTZ group and 3 (~2%) of the irbesartan + HCTZ group withdrew due to safety reasons; all were considered as related TEAEs.

No substantial differences between the two study drugs were observed in other safety parameters evaluated during study.

In conclusion, safety profile of zofenopril + HCTZ and irbesartan + HCTZ seems similar with the exception of hs-CRP values, decreased by zofenopril + HCTZ treatment and enhanced by irbesartan + HCTZ, the difference is statistically significant p=0.001. Even if hs-CRP determination was not included in safety parameters it important to underline the potential protective effect of zofenopril + HCTZ on vascular inflammation.

CONCLUSIONS

This study shows that zofenopril + hydrochlorothiazide combination is safe, well tolerated and effective as irbesartan + hydrochlorothiazide combination in reducing office sitting diastolic blood pressure in patients not controlled by previous monotherapy with one or more additional cardiovascular risk factors, even if the trend was always in favor of zofenopril + hydrochlorothiazide combination and in some subpopulations (e.g. moderate hypertension, and in patients receiving low dose, sub set #2) zofenopril + hydrochlorothiazide was significantly more effective than irbesartan + hydrochlorothiazide. The time course of sitting DBP reduction, induced by zofenopril + HCTZ and irbesartan + HCTZ, was similar at V1, after 6 days of administration, while within the time and after 18 weeks of administration the DBP reduction induced by zofenopril + HCTZ remains consistent and constant while the effect induced by irbesartan + HCTZ, slightly decreases within the time; similar results were obtained after 32 weeks of administration. Office sitting SBP was significantly and consistently reduced by both treatments even if the trend of reduction was in favour of irbesartan + HCTZ. The time course of sitting SBP reduction, induced by zofenopril + HCTZ and irbesartan + HCTZ, was similar at V1, after 6 days of administration, while within the time and after 18 weeks of administration the SBP reduction induced by zofenopril + HCTZ remains consistent and constant and was significantly higher than the effect induced by irbesartan + HCTZ, that slightly decreases within the time; similar results were obtained after 32 weeks of administration.Treatment with the zofenopril + HCTZ combination of hypertensive patients, having one or more additional cardiovascular risk factor, seems to provide a similar 6h and 24h blood pressure control, morning surge and SIs amelioration, as irbesartan + HCTZ, while AASI reduction was more consistent after zofenopril + HCTZ administration than after irbesartan + HCTZ, suggesting a better control of cardiovascular morbidity.
At last but not at least it must be also underlined a further zofenopril + HCTZ treatment added value, the potential protective effect on vascular inflammation, due to the ability of zofenopril + hydrochlorothiazide to reduce hs-CRP values.
No substantial differences between the two study drugs were observed in other safety parameters evaluated during study.
In conclusion, treatment with the zofenopril + HCTZ combination of hypertensive patients having one or more additional cardiovascular risk factor seems to provide a similar, but with a consistent trend of superiority reaching in some case the statistical significance, blood pressure control than irbesartan + HCTZ. In addition zofenopril + HCTZ combination offers the following added values: time course of DBP and SBP reduction more consistent and permanent within the time, a potential protective effect on vascular inflammation and a better control of cardiovascular morbidity. Safety profile of zofenopril + HCTZ and irbesartan + HCTZ seems similar.

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