2. SYNOPSIS

Title of Study:
Efficacy and safety of zofenopril + hydrochlorothiazide combination vs. irbesartan + hydrochlorothiazide combination in essential hypertensive patients not controlled by previous monotherapy

Double-blind, national multicentre, phase III study in essential hypertensive patients
Protocol number: LUMI/08/ZOF-001. EudraCT number: 2008-007681-30

Investigator(s): Coordinating Investigators [redacted]

List of Investigators: see Appendix 2.2

Study Center(s): 40 Italian.
List of sites see Appendix 2.2

Publication(s): Paragraph: 15

Studied Period: First patient enrolled: 27.05.2009
Last patient completed:10.01.2012

Clinical Phase: III

Objective(s):
- to determine whether the combination zofenopril + hydrochlorothiazide is at least as effective as the irbesartan + hydrochlorothiazide combination in normalizing or reducing office diastolic and systolic blood pressure in patients with essential hypertension, not controlled by a previous monotherapy and with one or more additional cardiovascular risk factors.

Methodology: non-inferiority trial with a randomized, double-blind, parallel group, controlled design. Following a run-in period of 2 weeks, patients were randomized to receive, once a day, in double-blind conditions either zofenopril 30 mg + hydrochlorothiazide 12.5 mg or irbesartan 150 mg + hydrochlorothiazide 12.5 mg for 18 weeks fixed combinations. After 6 or 12 weeks of treatment patients not controlled (SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg; SBP $\geq$ 130 mmHg and/or DBP $\geq$ 80 mmHg in diabetics or patients with at least 3 risk factors) were up-titrated to zofenopril 60 mg + hydrochlorothiazide 12.5 mg or irbesartan 300 mg + hydrochlorothiazide 12.5 mg. At the end of the 18 weeks of double-blind treatment only patients who already received up-titration at visit 1 or at visit 2, continued the double-blind extension of the study for additional 30 weeks with the same drug dosage used at visit 3b.

Number of Subjects:
Planned: about 446 randomised patients

Screened: 560 patients
Randomized: 462 patients (227 to zofenopril + hydrochlorothiazide and 235 to irbesartan + hydrochlorothiazide).
Treated (FAS): 434 patients (zofenopril + hydrochlorothiazide 213 and irbesartan + hydrochlorothiazide 221)
Completed - first study period (PP): 302 patients (zofenopril + hydrochlorothiazide 146 and irbesartan + hydrochlorothiazide 156)
Not receiving up-titration: 93 patients (zofenopril + hydrochlorothiazide 38 and irbesartan + hydrochlorothiazide 55)
Entered into extension phase: 244 patients (zofenopril + hydrochlorothiazide 130 and irbesartan + hydrochlorothiazide 114)
Completed - extension period (PP): 169 patients (zofenopril + hydrochlorothiazide 84 and irbesartan + hydrochlorothiazide 85)

Analyzed:
- Safety: 462 patients (zofenopril + hydrochlorothiazide 227 and irbesartan + hydrochlorothiazide 235)
- Efficacy (PP): 302 patients (zofenopril + hydrochlorothiazide 146 and irbesartan + hydrochlorothiazide 156)

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

- Outpatients aged 18-75 years
- Male and female gender
- Patients with essential hypertension currently taking one antihypertensive medication (ACE-inhibitor, AT1-

antagonist, calcium antagonist, diuretic or beta-blocker) in the last 3 months and not adequately controlled (office mean SBP ≥ 140 and/or DBP ≥ 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
  - Fasting plasma glucose 5.6–6.9 mmol/l (102–125 mg/dL) or on specific drug treatment for hyperglycemia
  - Diabetes mellitus: fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dL) or postload plasma glucose >11.0 mmol/l (198 mg/dL) or on specific drug treatment
  - Abdominal obesity: waist circumference >102 cm in males; >88 cm females or BMI ≥25 and ≤ 30 kg/m^2
  - Family history of premature cardiovascular disease (males at age <55 years; females at age <65 years)
- Able and willing to sing informed consent and to comply with study procedures
- Written informed consent of the patient

Investigational drug, 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: CTA0923 expiring November, 2011; CTC0930 expiring December, 201; CTI0915 expiring June, 2012
Zofenopril 30 mg encapsulated coated tablets once a day by oral route
Batch N: CTM0828 expiring October, 2011; CTC0919 expiring December, 2011; CTI0902 expiring June, 2012

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: CTN0815 expiring July, 2011;CTD0909 expiring November, 2011; CTF0917 expiring January, 2012
Irbesartan 150 mg encapsulated coated tablets once a day by oral route
Batch N: CTA0907 expiring July, 2011; CTD0923 expiring December, 2011; CTG909 expiring March, 2012

Duration of Treatment:
For the individual patient:
Run-in: 2 weeks Double-Blind Treatment: 18 weeks Extension Period: 30 weeks (Total: 50 weeks)
Global study duration:
Total recruitment period (first patient in to last patient in): 9 months
Study conduct (first patient in to last patient completed): 21 months

Criteria for Evaluation:
Main efficacy criteria

- Percentage of subjects with office sitting blood pressure <140/90 mmHg (<130/80 mmHg in diabetics or patients with at least 3 risk factors) or with an office 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 (responders).

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:
Efficacy parameter: the primary study end-point is the between-treatments comparison in the rate of responders.
Comparison between the two groups for the office sitting blood pressure (BP) change from baseline to the end of treatment was carried out by using a chi-square test: the 95% confidence interval (CI) of the difference in proportion was calculated and the lower bound compared with the 10% non-inferiority limit.
The Last Observations Carried Forward (LOCF) method was used to replace missing data for any cause. Binary

secondary efficacy endpoints was analysed using the same method.
The analytical model included the treatment factor and the baseline value as covariate; centre effect was included in the main model: if found significant, its interaction with treatment was investigated in a further exploratory model. The Last Observations Carried Forward (LOCF) method was used to replace missing data for any cause; the 95% confidence intervals (CI) for the difference in proportion were calculated and the lower bound compared with the 10% non-inferiority limit.
Both the FAS and the PPS were considered as the confirmatory sets.
Binary secondary efficacy endpoints were analyzed using the same method.
Comparison between the two groups for the secondary efficacy parameters were carried out by covariance analysis (ANCOVA).
The minimum level of statistical significance was set at 2.5% level (one sided two-group large-sample normal approximation test), with a power of 80%.

RESULTS:

Baseline characteristics
The patient population recruited in this study consisted in patients of both sexes, with a prevalence of males (56.2% vs 43.8% of female) and with a broad range of ages (22.7-78.2 years) with a similar median age in both study treatments. Most of the patients included were high risk patients (92.5% in the ZOF+HCTZ group and 92.3% in the IRB+HCTZ group) and in several cases had at least one concomitant disease (65.7% in the ZOF+HCTZ group and 60.2% in the IRB+HCTZ group) and, in several cases, were taking at least one concomitant medication (65.7% in the ZOF+HCTZ group and 55.1% in the IRB+HCTZ group).
There were no significant differences between the characteristics of the two treatment groups at entry.
The proportion of patients suffering from at least one concomitant disease was similar in the two treatment groups: in the ZOF+HCTZ group 96/146 patients (65.7%) vs 86/156 patients (55.1%) in the IRB+HCTZ group.
The most common concomitant diseases were: metabolism/endocrine disorders (50.7%), cardiovascular disorders (11.0%), gastrointestinal/hepatobiliary disorders (8.5%) and renal/urinary tract disorders (6.2%).
There were no important differences between the two treatment groups.
All patients, except one in the ZOF+HCTZ group and one in the IRB+HCTZ group were already on antihypertensive monotherapy treatment for hypertension, one patient in the ZOF+HCTZ group was already treated with politherapy for hypertension.
The most common previous therapies used for hypertension were: Triatec (ramipril) 12.9% and 11.8%; Norvasc (amlodipine) 5.8% and 6.5%; Lobivon (nebivolol) 5.8% and 8.3%; Enapren (enalapril) 9% and 5.9% ; Cardirene (acetylsalicylic acid) 3.2% and 4.7%; Approvel (ibersartan) 3.2% and 4.1% in ZOF+HCTZ and IRB+HCTZ group respectively. The most commonly used antihypertensive treatments were similarly distributed in the two treatment groups.
The proportion of patients who were taking concomitant medications until visit 3b was similar: 96/146 patients (65.7%) in the zofenopril + hydrochlorothiazide treatment group and 86/156 patients (55.1%) in the irbesartan + hydrochlorothiazide group.
The most common concomitant medications used until visit 3b were: Eutirox (levotiroxina) 3.6% and 4,3%; Crestor (rosuvastatina) 3.0% and 2.4% in ZOF+HCTZ and IRB+HCTZ group respectively. The most commonly used concomitant medications were similarly distributed in the two treatment groups.
A total of 244/302 patients received the up-titration 130 in the zofenopril + HCTZ group and 114 in the irbesartan + HCTZ group.

Efficacy
Primary endpoint
In the FAS, corrected by centre effect, the percentage of responder, i.e. decrease in office sitting BP, to zofenopril + HCTZ treated patients at V3b was 68.2% while in PPS , corrected by centre effect, the percentage of responder was 66.7%.
In FAS, corrected by centre effect, the percentage of responder, i.e. decrease in office sitting BP, to Irbesartan + HCTZ treated patients at V3b was 69.5% while in PPS , corrected by centre effect, the percentage of responder was 74.6%.
Analysis of covariance on changes from baseline to end of treatment (18 weeks), taking into account the baseline value and the centre effect, shows an estimate for the treatment difference (Zofenopril + HCTZ - Irbesartan + HCTZ) of 1.066 [95% CI: 0.685-1.659 p=0.778]: upper limit of the 95% confidence interval being inferior to the protocol defined non inferiority limit "the difference test-reference in rate of normalized patients less than 10%", non-inferiority criteria can be considered as reached by FAS analysis.
Analysis of covariance on changes from baseline to end of treatment (18 weeks), taking into account the baseline value and the centre effect, shows an estimate for the treatment difference (Zofenopril + HCTZ - Irbesartan + HCTZ) of 1.469 [95% CI: 0.846 -2.551 p=0.171]: upper limit of the 95% confidence interval being inferior to the protocol defined non inferiority limit "the difference test-reference in rate of normalized patients less than 10%", non-inferiority criteria can be considered as reached also by PPS analysis.
The rate of DBP and SBP responders over the 24 hours was high in both treatment groups, similar results were obtained after Zofenopril (84.5% of patients at low dose and 83.5% at higher dose) and Irbesartan (81.9% of patients at low dose and 82.1% at higher dose) administered for 18 weeks.
When a subgroup of patients with mild hypertension was considered the percentage of responder was similar in both groups; responders 66.4% by FAS and 66.0% by PPS for Zofenopril + HCTZ and 67.7% by FAS and 73.3% by PPS Irbesartan + HCTZ. Treatment differences estimated were 1,061 [95% CI: 0,656 – 1,716: p=0.810] by FA

set and 1,412 [95% CI: 0,771 – 2,584: p=0.263] by PP set at week 18.
When a subgroup of patients with moderate hypertension was considered the percentage of responder was again similar in both groups; responders 75.8% by FAS and 70.0 by PPS for Zofenopril + HCTZ and 78.1% by FAS and 80.0% by PPS Irbesartan + HCTZ. Treatment differences estimated were 1.577 [95% CI: 0.360 – 3.631: p=0.821] by FA set and 1,714 [95% CI: 0,436 – 6,742 p=0.438] by PP set at week 18.
Again non inferiority criteria were satisfied with upper bound of the CI less than the pre-defined non inferiority limit.

Secondary endpoints first study period:

- Rate of normalized patient: BP decreases similarly and consistently in both groups, no statistical difference was found in the percentage of normalized patients between groups under study.
- Office sitting DBP change after 18 weeks: DBP was consistently decreased by both treatments from visit 0 to Visit 3b. The effects of Irbesartan + HCTZ treatment on DBP time course and on the Δ of improvement were significantly higher at V3b ($p<0.05$). In spite of this the Δ of improvement, V0 - V3b 10.7 and 12.34 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ, was similar and,from a clinical point of view, was not substantially different indicating that both drugs exerted a similar effect. Moreover after 48 weeks of treatment Zofenopril + HCTZ and Irbesartan + HCTZ effects on DBP were comparable and not statistically different.
- Office sitting SBP change after 18 weeks: SBP was consistently decreased by both treatments from visit 0 to Visit 3b. The effects of Irbesartan + HCTZ treatment on SBP time course and on the Δ of improvement were significantly higher at V3b ($p<0.05$). In spite of this the Δ of improvement, V0 - V3b 15.67 and 18.48 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ, was similar and, from a clinical point of view, was not substantially different indicating that both drugs exerted a similar effect. Moreover after 48 weeks of treatment Zofenopril + HCTZ and Irbesartan + HCTZ effects on SBP were comparable and not statistically different.
- Zofenopril + HCTZ and Irbesartan + HCTZ had a similar effect on office SBP changes after 18 weeks of treatment, while office DBP changes were slightly but significantly higher in the Irbesartan treated group.
- 24 hour mean SBP changes after 18 weeks of treatment were slightly significantly different between the two treatment groups, while these parameters were not different when centre effect and high drug dose were considered, indicating that Zofenopril + HCTZ - Irbesartan + HCTZ were similarly effective.
- 24 hour mean DBP changes after 18 weeks of treatment were significantly higher in the Irbesartan group for all the subgroups explored.
- Average hourly values were consistently reduced by both treatment regimes in the ITT and in the PP population. Daily trend was similar indicating that daily pressure variations were similarly compensate bay both treatments after 18 weeks of administration.
- The magnitude of the morning surge was similarly reduced by both treatment groups after 18 weeks of treatment. Morning surge prevalence was similar in the two groups under study after 18 weeks of administration.
- Smoothness Index of SBP and DBP after 18 weeks of treatment, considering centre effect and high dose, was non-statistically different between the two treatment groups after 18 weeks of treatment.
- Change in LVMI [g/m2] (echocardiography) after 18 weeks: the improvement of LVMI at V3b seems to be significantly higher in the Irbesartan + HCTZ however the baseline values were higher in the Irbesartan + HCTZ group than in the Zofenopril + HCTZ. Indeed the Δ of improvement of LVMI [g/m2](from V0 to V3b was similar in both study groups (by FAS and PPS by Zofenopril + HCTZ and Irbesartan + HCTZ respectively) and no statistical difference was found, indicating that both drugs had a similar effect in normalizing LVMI.
- Change in LVMI [g/h] (echocardiography) after 18 weeks: the improvement of LVMI [g/h] from V0 to V3b was similar in both study groups and no statistical difference was found (V0 55.56 and 60.55 V3b 53.57 and 56.06 by FAS ; V0 56.81 and 60.18 V3b 54.30 and 54.46 by Zofenopril + HCTZ and Irbesartan + HCTZ respectively), indicating that both drugs had a similar effect in normalizing LVMI.
- Rate of patients with LVH by echocardiography after 18 weeks: the rate of LVH improvement, LVH regression, at V3b was similar in both groups and both drugs showed a similar effect in normalizing LVH value at V3b (V0: 52.7 and 54.4 ; V3b: 58.3 and 63.2 by FAS; V0: 51.4 and 54.8 ; V3b: 56.9 and 62.2 by PPS for Irbesartan + HCTZ and Zofenopril + HCTZ respectively). Obtained improvements were similar and not statistically different.
- Rate of patients with LVH as detected by ECG after 18 weeks: in the Zofenopril + HCTZ treated group both analytical sets, FAS and PPS, indicate a complete regression of LVH, while the effect induced by Irbesartan + HCTZ was slithery lower at V3b (V0 versus V3b : 2.4% and 0.0% by FAS and 2.1% and 0.0% by PPS ; 2.8% and 1.1% by FAS and 2.6% and 1.4% by PPS for Zofenopril + HCTZ and Irbesartan + HCTZ respectively).
- Results obtained were also confirmed by three new criteria recommended to be used as present standards; results obtained by all the 3 new criteria always indicate, and confirmed, the positive trend in favour of Zofenopril + HCTZ.
- Change in right and left carotid IMT after 18 weeks: IMT was not significantly affected by treatments.
- Rate of patients with right or left carotid plaque after 18 weeks (IMT > 1,3 mm in any district evaluated): Zofenopril + HCTZ treatment consistently reduced the percentage of patients with carotid

plaques; Irbesartan + HCTZ treatment did not modify the baseline value.

- Rate of patients with thickness radius (h/R), after 18 weeks: the rate of normalized patients was improved by Zofenopril + HCTZ treatment (V0 21.2% and V3b 26.0%) whereas was slightly reduced by Irbesartan + HCTZ treatment (V0 28.8% and V3b 27.6%); on the contrary the rate of not normalized patients was lowered by Zofenopril + HCTZ treatment (V0 74.7% and V3b 67.8%) while was only slightly modified in the Irbesartan + HCTZ group (V0 69.9% and V3b 66.7%).
- Rate of patients with reduced renal function and renal damage after 18 weeks:
  - Changes in creatinine clearance after 18 weeks: creatinine clearance was not substantially modified after Zofenopril + HCTZ and Irbesartan + HCTZ administration for 18 weeks.
  - Zofenopril + HCTZ and Irbesartan + HCTZ similarly reduced the percentage of patients with proteins detected in urine at V3b versus baseline.
  - Rate of patients with reduced renal function, cratinine clearance > 60ml/min, after 18 weeks: the ratio of patients with normal renal functions was not modified after Zofenopril + HCTZ and Irbesartan + HCTZ.
  - Zofenopril + HCTZ consistently reduced the percentage of patients with renal damage, albumin-creatinine ratio > 22 for men and > 31 for women or microalbuminuria between 30 and 300 mg/24h or semiquantitative assessment of microalbuminuria by urine dipstick, Irbesartan + HCTZ showed a similar trend but was less effective.

Secondary endpoints: first study period patients not performing up-titration

- Percentage of responders' patients with office sitting blood pressure <140/90 mmHg (<130/80 mmHg in diabetics or patients with at least 3 risk factors) after 18 weeks of treatment was similar in the two study groups: responders 76.4% and 78.9% for Zofenopril + HCTZ and Irbesartan + HCTZ treatment respectively indicating a similar effect. Treatment differences estimated 1.159 [95% CI: 0.4556 – 2.415: p= 0.693]; non inferiority criteria were satisfied with upper bound of the CI less than the pre-defined non inferiority limit.
- When a subgroup of patients with mild hypertension was considered the percentage of responder was similar in the two study groups: responders 74.6% and 78.8% for Zofenopril + HCTZ and Irbesartan + HCTZ treatment respectively indicating a similar effect. Treatment differences estimated was 1,267 [95% CI: 0.587 – 2.736: p=0.546]; non inferiority criteria were satisfied with upper bound of the CI less than the pre-defined non inferiority limit.
- When a subgroup of patients with moderate hypertension was considered the percentage of responder was consistently higher in the Zofenopril + HCTZ group: responders 88.9% and 80.0% for Zofenopril + HCTZ and Irbesartan + HCTZ treatment respectively; results obtained support the higher effect of Zofenopril + HCTZ in reducing hypertension in a subgroup of patients with moderate hypertension treated for 18 weeks with zofenopril 30 mg + hydrochlorothiazide 12.5 mg .
- Rate of subjects with office sitting blood pressure <140/90 mmHg after 18 weeks (responders): both Zofenopril + HCTZ and Irbesartan + HCTZ had a similar effect in the rate of treatment response as well as in non-responder's one; confirming that the two treatments had similar effect in normalizing office sitting BP with a trend in favour of Irbesartan + HCTZ.
- Office sitting DBP change after 18 weeks: DBP was consistently and similarly decreased by both treatments from visit 0 to Visit 3b. The effects of Irbesartan + HCTZ treatment on DBP time course and in the Δ of improvement were similar and not significantly different. The Δ of improvement, V0 - V3b 12.67 and 15.17 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ, were on the same range; moreover in both case normal values were reached at V3b 78.58 and 76.40 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ.
- Office sitting SBP change after 18 weeks: SBP was consistently and similarly decreased by both treatments from visit 0 to Visit 3b, the only borderline statistical difference was observed on SBP time course by FA set ($p<0.05$) . In spite of this the effects of Irbesartan + HCTZ treatment on SBP time course and on the Δ of improvement were similar. The Δ of improvement, V0 - V3b 19.51 and 22.50 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ, were comparable; moreover in both case normal values were reached at V3b 126.53 and 123.41 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ.
- Changes in LVMI, IMT, creatinine clearance and urinary protein after 18 weeks:
  - LVMI improvement, evaluated as [g/m2] and [g/h], was similar in Zofenopril + HCTZ and in Irbesartan + HCTZ groups.
  - Change in right and left carotid IMT after 18 weeks: IMT was not significantly affected by the treatments.
  - Rate of patients with LVH by echocardiography and ECG after 18 weeks:
    - LVH values, detected by echocardiography, were reduced by drug treatment, from baseline to visit 3, with a trend in favour of Irbesartan + HCTZ.
    - LVH values, detected by ECG, were reduced by drug treatment, from baseline to visit 3, with a trend in favour of Zofenopril + HCTZ.

  Results obtained confirm that both drugs were capable to similarly reduce the rate of patients with LVH.
  - Rate of patients with carotid plaque after 18 weeks (IMT > 1,3 mm in any district evaluated): In the right carotid both treatments reduces the percentage of patients with carotid plaques; Zofenopril + HCTZ treatment was more effective. In the left carotid the percentage of patients

with carotid plaques was reduced by Zofenopril + HCTZ and not modified by Irbesartan + HCTZ. In the right or left carotid Zofenopril + HCTZ treatment consistently reduced the percentage of patients with carotid plaques while Irbesartan + HCTZ was only slightly effective.

- Rate of patients with thickness radius (h/R) 18 weeks: that rate of normalized patients was slithery reduced by the Zofenopril + HCTZ treatment (22.4% at V0 and 15.3% at V3b) while the rate of normalized patients was slithery increased by Irbesartan + HCTZ treatment (29.4% at V0 and 35.8% at V3b). This result is not in line with the global study results obtained at V3b and at V 7b probably because of the low number of patients evaluated by the subgroup. By the way it must be underlined that the rate of concentric remodelling was consistently increased by Zofenopril + HCTZ treatment (27.6% at V0 and 44.1% at V3b) while only slightly improved by Irbesartan + HCTZ treatment (28.4% at V0 and 34.6% at V3b).
- Rate of patients with reduced renal function and renal damage after 18 weeks:
  - creatinine clearance was not substantially modified after Zofenopril + HCTZ and Irbesartan + HCTZ administration for 18 weeks.
  - Zofenopril + HCTZ consistently reduced the percentage of patients with proteins detected in urine (V0 30.4% and V3b 19.3%) while Irbesartan + HCTZ did not substantially modify this parameter (V0 22.9% and V3b 20.7%).
  - The rate of patient with reduced renal function, cratinine clearance > 60ml/min, was slightly increased by Zofenopril + HCTZ (V0 8.5% and V3b 13.8%); Irbesartan + HCTZ administration also increased the rate of patient with reduced renal function (V0 5.7% and V3b 7.3%)but with slithery lower effect. Results obtained were not statistically significant indicating that changes were not consistent.
  - The rate of patients with renal damage, albumin-creatinine ratio > 22 for men and > 31 for women or microalbuminuria between 30 and 300 mg/24h or semiquantitative assessment of microalbuminuria by urine dipstick, was consistently reduced after Zofenopril + HCTZ (V0 50.8% and V3b 11.6%) similar results were observed after Irbesartan + HCTZ (V0 49.3% and V3b 3.4%). Results obtained were not statistically different indicating that the effect obtained after drugs administration was similar.

Secondary endpoints patients performing extension phase:

- Percentage of normalised subjects with office sitting blood pressure <140/90 mmHg (<130/80 mmHg in diabetics or patients with at least 3 risk factors) after 48 weeks: Treatment differences estimated 0.844 [95% CI: 0.466 – 1.528: p= 0.575] by FAS and 0.857 [95% CI: 0.434 – 1.693: p =0.657] by PPS, confirming that the two treatments had similar effect in normalizing office sitting blood pressure after 48 weeks of treatment and that the non-inferiority criteria was satisfied.
- Office sitting DBP change after 48 weeks: DBP was consistently and similarly decreased by both treatments from visit 0 to Visit 7b. The effects of Irbesartan + HCTZ treatment on DBP time course and in the Δ of improvement were similar and not significantly different. The Δ of improvement, V0 – V7b 12.23 and 12.46 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ, were on the same range; moreover in both case normal values were reached at V7b 80.48 and 79.00 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ.
- Office sitting SBP change after 48 weeks: SBP was consistently and similarly decreased by both treatments from visit 0 to Visit 7b. The effects of Irbesartan + HCTZ treatment on SBP time course and on the Δ of improvement were similar. The Δ of improvement, V0 – V7 b 19.05 and 19.49 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ, were comparable; moreover in both case normal values were reached at V7b 131.41 and 130.24 respectively for Zofenopril + HCTZ and Irbesartan + HCTZ.
- Baseline adjusted SBP and DBP changes after 48 weeks of treatment were similar between the two treatment groups indicating that Zofenopril + HCTZ - Irbesartan + HCTZ were similarly effective on 24 hour SBP and DBP changes after 48 weeks of treatment
- Rate of subjects with office sitting blood pressure <140/90 mmHg after 48 weeks (responders): both Zofenopril + HCTZ and Irbesartan + HCTZ had a similar effect in the rate of treatment responders as well as in non-responder's one; confirming that the two treatments had similar effect in normalizing office sitting BP.
- Changes in LVMI, IMT, creatinine clearance and urinary protein after 48 weeks:
  - LVMI final improvement was similar in both treatment groups after 48 weeks of treatment:
    - Change in LVMI [g/m2] (echocardiography) after 48 weeks: the improvement of LVMI at V7b seems to be significantly higher in the Irbesartan + HCTZ however the baseline values were higher in the Irbesartan + HCTZ group than in the Zofenopril + HCTZ. Indeed the Δ of improvement of LVMI [g/m2](from V0 to V7b) was similar in both study groups (13.41 and 16.31 by FAS and 16.90 and 16.39 by PPS after Zofenopril + HCTZ and Irbesartan + HCTZ respectively) and no statistical difference was found, indicating that both drugs had a similar effect in normalizing LVMI.
    - Change in LVMI [g/h] (echocardiography) after 48 weeks: the improvement of LVMI [g/h] from V0 to V7b was similar in both study groups and not statistically

different for PPS (V0 56.50 and 64.03; V7b 53.95 and 54.68 by FAS ; V0 57.96 and 66.38; V7b 55.70 and 57.36 by PPS after Zofenopril + HCTZ and Irbesartan + HCTZ respectively), indicating that both drugs had a similar effect in normalizing LVMI even if Irbesartan + HCTZ LVMI values were higher at V0.

- Change in right and left carotid IMT after 48 weeks: IMT was not significantly affected by the treatments even if Zofenopril + HCTZ treatment was more effective in reducing IMT.
- Rate of patients with LVH by echocardiography and ECG after 48 weeks: both treatments were capable of consistently reduce/normalize at V7b the rate of patients with LVH detected by echocardiography and ECG.
- Rate of patients with carotid plaque after 48 weeks (IMT > 1,3 mm in any district evaluated): in the right carotid both treatments reduces the percentage of patients with carotid plaques; Zofenopril + HCTZ treatment was more effective. In the left carotid the percentage of patients with carotid plaques was not modified by treatments.
- Rate of patients with thickness radius (h/R) after 48 weeks: that rate of normalized patients was consistently increased by the Zofenopril + HCTZ treatment (V0 23.8% and V7b 28.6%) whereas the rate of normalized patients was reduced by Irbesartan + HCTZ treatment (V0 27.1% and V7b 22.4%); on the contrary the rate of not normalized patients was consistently lowered by Zofenopril + HCTZ treatment (V0 72.6% and V7b 59.5%) while was only slightly modified in the Irbesartan + HCTZ group (V0 72.9% and V3b 68.2%).
- Rate of patients with reduced renal function and renal damage after 48 weeks:
  - Zofenopril + HCTZ did not modify or slithery improved creatinine clearance increasing values at V7b versus baseline (+0,44 by FAS and +1,91 by PPS at V7b) whereas Irbesartan + HCTZ consistently affected the creatinine clearance at V7b versus baseline (-7,82 by FAS and -8,70 by PPS at V7b).
  - Zofenopril + HCTZ and Irbesartan + HCTZ treatments did not affect the percentage of patients with proteins detected in urine.
  - The rate of patient with normal renal function, creatinine clearance >60 mL/min, was slightly increased after Zofenopril + HCTZ (V0 91.6 and V7b 95.9) whereas was consistently reduced after Irbesartan + HCTZ (V0 91.8 and V7b 80.9).Similarly the rate of patient with reduced renal function was reduced by Zofenopril + HCTZ (V0 8.4 and V7b 4.1) whereas was consistently increased after Irbesartan + HCTZ (V0 8.2 and V7b 19.1).
  - The rate of patients with renal damage, albumin-creatinine ratio > 22 for men and > 31 for women or microalbuminuria between 30 and 300 mg/24h or semiquantitative assessment of microalbuminuria by urine dipstick: the rate of patients with no renal damage was similarly and consistently increased after Zofenopril + HCTZ and Irbesartan + HCTZ.

Safety:

Four hundreds and sixty-two (462) patients were included in the Safety Set: 227 and 235 of which received zofenopril + HCTZ and irbesartan + HCTZ respectively.

During the period baseline to visit 3b a total of 62 patients, 37 (16.3%) in the zofenopril + HCTZ group and of 25 patients (10.6%) in the irbesartan + HCTZ group, reported at least one treatment-emergent adverse event. A total of 24 patients, 17 (70.8%) in the zofenopril + HCTZ group and 7 patients (29.2%) 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).

Three patients (100%) in the zofenopril + HCTZ group reported at least one serious adverse event (SAE) during the study period baseline-V3b; no serious AE was reported in the irbesartan + HCTZ group during the study period baseline-V3b; none of the 6 events recorded in the zofenopril + HCTZ group until V-3b was considered by the investigator as related to study treatment.

A total of 18 patients, 14 (77.8%) in the zofenopril + HCTZ group and 4 patients (22.2%) in the irbesartan + HCTZ group, withdrew due to safety reasons; all were considered as related TEAEs during the study period baseline-V3b.

During the period 3b to visit 7b a total of 29 patients, 16 (7.0 %) in the zofenopril + HCTZ group and of 13 patients (5.5%) in the irbesartan + HCTZ group, reported at least one treatment-emergent adverse event.

A total of 9 patients, 5 (71.4%) in the zofenopril + HCTZ group and 4 patients (44.5%) 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).

During the period 3b to visit 7b a total of 3 patients reported at least one SAE, 2 (66,6%) in the zofenopril + HCTZ group and 1 (33,3%) in the irbesartan + HCTZ group; one of the events, hyperkalemia, was considered by the investigator as probably related to study treatment, zofenopril.

A total of 2 patients (100%) in the zofenopril + HCTZ group withdrew due to safety reasons; one event wasconsidered as related TEAE.

CONCLUSIONS:

This study shows that zofenopril + hydrochlorothiazide fixed combination is safe, well tolerated and at least as effective as irbesartan + hydrochlorothiazide fixed combination in reducing the percentage of subjects whit essential hypertension not controlled by previous monotherapy, with one or more additional cardiovascular risk factors. Moreover results obtained underline that the hourly average changes were consistently and similarly modulated by both treatments administered.
Furthermore zofenopril + hydrochlorothiazide effect on ABMP is persistent within time and, after 48 weeks zofenopril + hydrochlorothiazide and irbesartan + hydrochlorothiazide administration, the effect of the two administered drugs on ABMP is similar.

Zofenopril + hydrochlorothiazide is more effective than irbesartan + hydrochlorothiazide in reducing thickness of chamber radius, in reducing the percentage of patients with right or left carotid plaque and in improving renal function. These results deserve more comments:

1) The reduction of right or left carotid plaque shown by zofenopril (already demonstrated in other studies done in hypertensive patients) may be justified by the pharmacokinetic characteristics of zofenopril (sulphidryl group and higher lipophilicity) as the Blood Pressure reduction was similar in both study groups.
2) The improvement in renal function demonstrated by zofenopril (especially at 48 weeks) is a very interesting result as the comparator (Irbesartan) has shown in previous studies to be the best drug of his class in reducing renal damage. Again the explanation may be found in the intrinsic characteristics of zofenopril as the Blood Pressure reduction was similar in both study groups.

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