This Synopsis 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 not be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

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

2. SYNOPSIS

Title of Study: Comparison between Zofenopril and Ramipril in combination with ASA on the extent of cardiovascular risk in patients with systolic left ventricular dysfunction after acute myocardial infarction. (SMILE IV TRIAL)

Protocol number: MEN/03/ZOF-CHF/001
EudraCT number 2004-001150-88

Investigator(s): Coordinating Investigators :
[redacted]

Study Center(s): 79 sites (Coronary Units or Departments of Cardiology or Internal Medicine) with at least 100 hospitalized acute MI patients/year) in 8 countries: Italy, Greece, Portugal, Spain, Turkey, Romania, Russia and Ukraine.

Studied Period: First patient enrolled: 15/03/2005 (Am. 1) Last patient completed: 22/07/2009	**Clinical Phase:** IIIb

Objective(s):
Primary:

- to demonstrate the efficacy of Zofenopril associated to ASA 100 mg/day on the prevention of cardiovascular mortality and morbidity in comparison with Ramipril associated to ASA 100 mg/day in patients with systolic left ventricular dysfunction after acute myocardial infarction.

Secondary:

- to evaluate the individual tolerability of different drug combinations;
- to evaluate changes in left ventricular remodeling.

Methodology: randomized, double-blind, controlled trial carried out in parallel groups of patients with post-MI systolic LV dysfunction. Following an open phase period of 4 days (titration period - from day 1 to day 4) during which all the patients were treated with Zofenopril at increasing dosage and ASA 100 mg/day, patients were randomized to receive in double-blind conditions either Zofenopril 30 mg bid or Ramipril 5 mg bid plus ASA 100 mg/day (from day 5 to month 12).

Number of Subjects:

Planned: 896 randomised patients

Screened/enrolled : 871 patients
Randomized: 771 patients (389 to Zofenopril +ASA and 382 to Ramipril + ASA)

Completed treatment phase: 518 patients (262 to Zofenopril +ASA and 256 to Ramipril + ASA)

Analyzed
- Safety: 768 patients (Zofenopril +ASA 388 and Ramipril + ASA 380)

- Efficacy : FAS population: 716 patients (Zofenopril +ASA 365 and Ramipril + ASA 351)
PP population: 594 patients (Zofenopril +ASA 301 and Ramipril + ASA 293)

Diagnosis and Criteria for Inclusion:
Eligibility criteria (at day 1) in final protocol and Amendment 1
Patients meeting the following eligibility criteria (at day 1) were included:
a) Written informed consent of the patient
b) Male and female aged 18-85 years
c) Patient suffering from acute myocardial infarction during the 24 hours before inclusion in the study and treated or not with thrombolytic drugs in the previous 12 hours.
Inclusion criterion "a" (at day 5)
Acute myocardial infarction with clinical (Killip class > 1, NYHA class > I, combination of 3"1 heart sound + pulmonary rales + pulmonary congestion on chest X-ray) or echocardiographic (LVEF < 45%) evidence of systolic LV dysfunction.

Eligibility criteria (at day 1) according to Amendment 2
The "c" criterion was changed as follows:
c) Patient suffering from ST-segment elevation acute myocardial infarction, during the 24 hours before inclusion in the study, with clinical (i.e. Killip class > 1, and combination with at least one of the following criteria: 3" heart sound or pulmonary congestion on chest X-ray) or echocardiographic (i.e. LVEF < 45%) evidence of systolic LV dysfunction.
Inclusion criterion "a" (at day 5) was changed as follows:
Patient suffering from ST-segment elevation acute myocardial infarction, during the 24 hours before inclusion in the study, with clinical (i.e. Killip class > 1, and combination with at least one of the following criteria: 3" heart sound or pulmonary congestion on chest X-ray) or echocardiographic (i.e. LVEF < 45%) evidence of systolic LV dysfunction.

Eligibility criteria (at day 1) according to Amendment 3
The "c" criterion was changed as follows:
c) Patient suffering from ST-segment elevation acute myocardial infarction (STEMI or NSTEMI) during the 24 hours before inclusion in the study, with clinical (i.e. Killip class > 1, and combination with at least one of the following criteria: 3" heart sound or pulmonary congestion on chest X-ray) and/or echocardiographic (i.e. LVEF < 45%) evidence of systolic LV dysfunction.
Inclusion criterion "a" (at day 5) was deleted.

3 patients were enrolled according to eligibility criteria of Amendment 1; 75 patients were enrolled according to eligibility criteria of Amendment 2 and all remaining patients were enrolled according to Amendment 3.

Test Product, Dose, Mode of Administration, Batch No(s):
Zofenopril 7.5 mg tablets bid , i.e. 15 mg daily, by oral route.
Zofenopril 15 mg tablets bid , i.e. 30 mg daily, by oral route.
Zofenopril 30 mg capsules bid , i.e. 60 mg daily, by oral route.
ASA 100 mg tablets od, i.e. 100 mg daily, by oral route.
Batch numbers are listed in Appendix 16.1.6

Duration of Treatment:
For the individual patient:
Open phase: 4 days
Double blind phase from day 5 to month 12: 12 months
Global study duration:
Total recruitment period (first patient in to last patient in): 39 months
Study conduct (last patient in to last patient completed): 12 months
Total study duration: about 51 months

Reference Therapy, Dose, Mode of Administration, Batch No(s):
Ramipril 5 mg capsules bid, i.e. 10 mg daily, by oral route
ASA 100 mg tablets od, by oral route.
Batch numbers are listed in Appendix 16.1.6

Criteria for Evaluation:
Main efficacy criteria

Efficacy variables:
Primary end point:
- One-year cardiovascular mortality and morbidity (one-year hospitalization for CV causes)

Secondary end points

- One-year cardiovascular mortality
- One-year hospitalization for cardiovascular causes
- Changes of LV ejection fraction
- Changes in LV end-diastolic and end-systolic volumes
- Changes of plasma NT-pro BNP levels

Safety criteria

- Overall incidence of non cardiovascular adverse events
- Occurrence of hypotension
- Laboratory parameters
- Deterioration of renal function (decline > 15% of GFR, according to the Cockroft-Gault formula)
- Vital Signs (SBP, DBP, HR)

Statistical Methods:

Analysis of efficacy

The primary endpoint was to assess the one-year cardiovascular mortality and morbidity (one- year hospitalization for CV causes) and the confirmatory analysis of efficacy was focused on the paired comparison of the treatment groups (a. Zofenopril + ASA 100 mg/day; b. Ramipril + ASA 100 mg/day). Two populations were defined for the analysis of efficacy data: the FAS (Full Analysis Set) population and the PP (per protocol) population and the same analysis were carried out for both. A logistic regression model was used to assess differences between treatment groups with respect to the cardiovascular mortality and morbidity rate.

In order to account for the heterogeneity of the treatment effect from center to center, and for various known or suspected risk factors, co-factors including center were considered for inclusion in the statistical model using a stepwise procedure with a significance level for entry of 0.10 and for staying of 0.10, whereas treatment effect (Zofenopril or Ramipril) was forced in the model. Any eventual rule for combining centers was specified before unblinding. The Wald test was used to test for the null hypothesis of no difference between treatment groups. The estimated Relative Risk and its corresponding 95% confidence intervals were derived from the model. Kaplan-Meier survival plots were provided to display event-free survival times for each treatment group.

Secondary efficacy endpoints: one-year cardiovascular mortality, one-year hospitalization for CV cause were analyzed as described above. The incidence of each CV event occurring during the study was displayed in frequency tables and compared between groups. Time course of NT-pro BNP and of echocardiography parameters and relative changes versus baseline were displayed using descriptive statistics and plots over time. Differences between groups on the last assessed value were analyzed by means of an analysis of covariance (ANCOVA) including the baseline value as a covariate in the model.

Safety data were analysed descriptively.

RESULTS:

Baseline characteristics

There were no relevant differences between the treatment groups in demographic and baseline characteristics.

In the FAS Population the treatment groups appear to be well balanced for gender (73.4% male in the Zofenopril group vs 78.6% in the Ramipril one), age (mean age 61 in both groups range 26-86 years), AMI localization with more than the 50% of the patients with an anterior localisation in both groups, Killip classification (about 60% classified as Killip 2 in both groups and 32-34% as Killip 1 in the zofenopril-ramipril groups), BMI patient's habits and disease characteristics.

Most of the patients presented hypertension requiring treatment: slightly more in the Zofenopril group (67.9 %) than in the Ramipril one (60.1%); other CV medical conditions are homogeneous across treatment groups.

38.4% of patients in both groups had a thrombolitic therapy. About 30% in both groups performed PTCA and almost all patients had an evidence of left ventricular disfunction.

As for concomitant therapies, 95% of patients had at least one CV system related concomitant therapy and there is no evidence of any imbalance across treatment groups.

Co-factors considered as prognostic for study treatment efficacy appear to be well distributed across treatment groups.

Efficacy

Primary endpoint:

FAS Population

One hundred five (105) patients in Zofenopril group and one hundred twenty-eight (128) patients in the Ramipril reached the primary endpoint defined as the occurrence of cardiovascular mortality or morbidity: this corresponds to a rate of 28.8% in the Zofenopril group vs 36.5% in the Ramipril group leading to a -7.7 % difference in favour of Zofenopril.

Table I – Primary endpoint: cardiovascular mortality and morbidity rate (FAS)

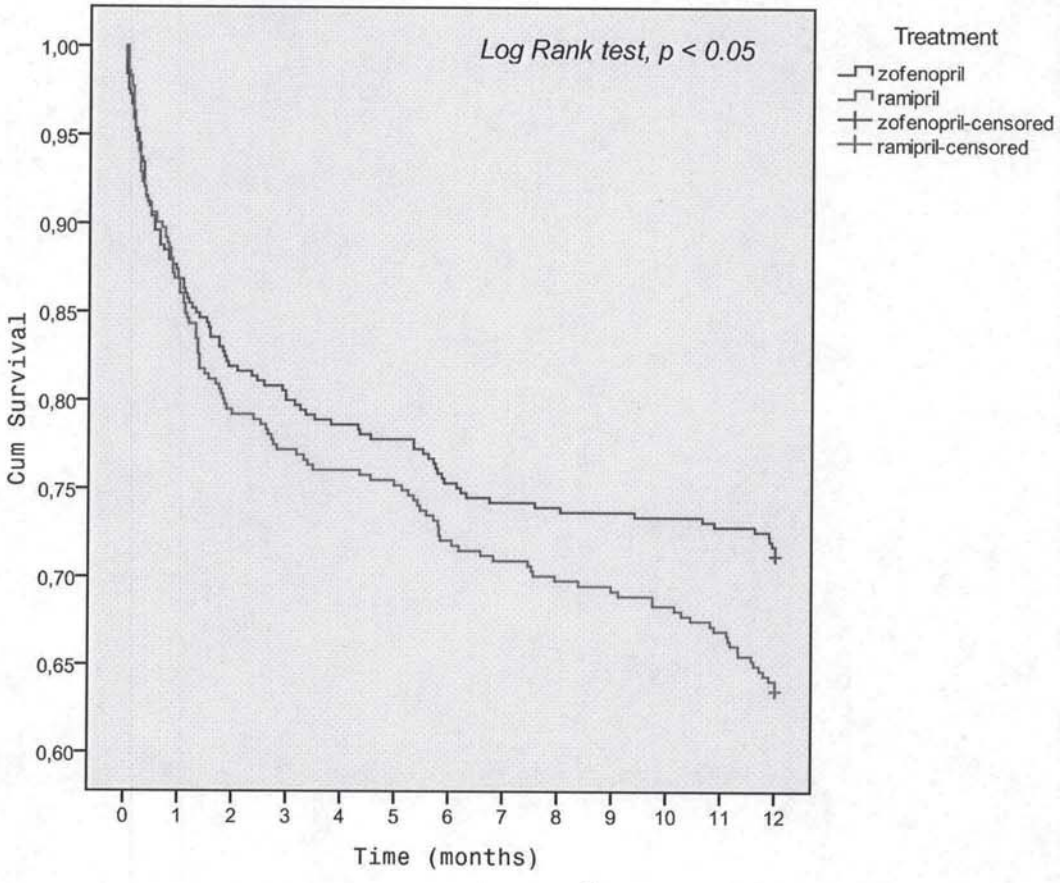
Analysis		Estimate [95% CI]
Event Rate	Zofenopril (105/365)	28.8% [24.1% ; 33.4%]
	Ramipril (128/351)	36.5% [31.4% ; 42.5%]
Logistic Regression	Odds Ratio Zofenopril vs Ramipril	0.704 [0.514 ; 0.963] p = **0.028**
Time to event: Cox Proportional Hazard Model	Hazard Ratio	0.741 [0.569 ; 0.964]

Prognostic factors in the logistic regression model during the stepwise selection show a significant influence on the results of the following covariates: LVEF ($p < 0.05$), Killip Class ($p < 0.05$), Revascularization ($p < 0.001$), Type of Infarction ($p < 0.05$) and Low HDL ($p < 0.05$). Treatment effect was significant ($p < 0.05$) and the Odds Ratio (Zofenopril vs Ramipril) was equal to 0.684 (95% IC = 0.492 – 0.952). None of the selected prognostic factors has shown any significant interaction with treatment.

Time to event was additionally analysed using a Cox Proportional Hazard Model with a stepwise selection of the relevant covariates: again treatment effect was found to be significant ($p < 0.05$) with a Hazard Ratio = 0.758 (95% IC = 0.580 – 0.991).

Event-free Survival time displayed by means of a Kaplan-Meier Plot in Figure I shows a significant difference (Log Rank test, $p<0.05$) in favour of Zofenopril.

Figure 1. Time to primary endpoint – Kaplan Meier plot (FAS).



PPS population
Logistic regression analysis performed on the 594 patients of the Per-Protocol set lead to similar results with 87/301 (28.9 %) events in the Zofenopril group and 102/293 (34.8%) in the Ramipril one with an odds ratio of 0.716 [0.538 ; 1.076] (p = 0.122).

Prognostic factors in the logistic regression model during the stepwise selection show a significant influence on the results of the following covariates: LVEF ($p < 0.05$), Revascularization ($p < 0.01$), Type of Infarction ($p < 0.05$) and Hypercholesterolemia ($p < 0.05$). Treatment effect was not significant (p = 0.083) and the Odds Ratio (Zofenopril vs Ramipril) was equal to 0.722 (95% IC = 0.499 – 1.044). None of the selected prognostic factors has shown any significant interaction with treatment.

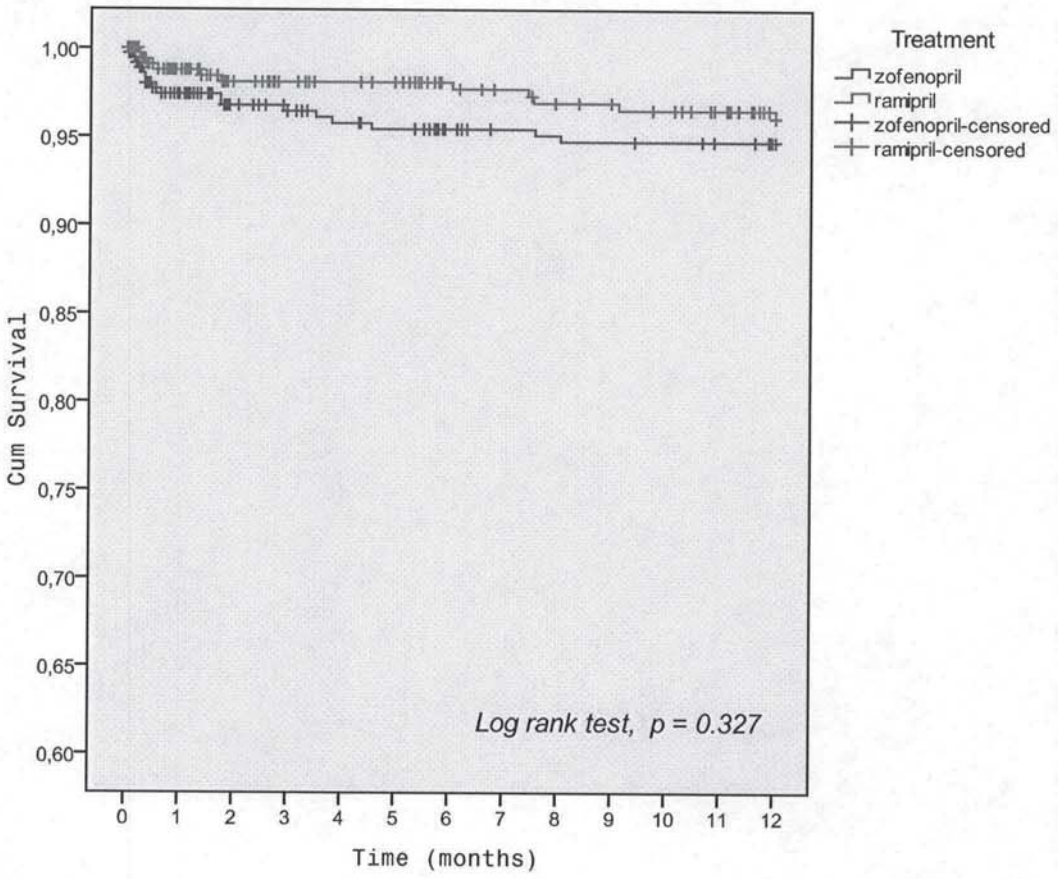
Time to event was also analysed using a Cox Proportional Hazard Model with a stepwise selection of the relevant covariates: again treatment effect was found to be not significant (p = 0.116) with a Hazard Ratio = 0.787 (95% IC = 0.583 – 1.062).

Secondary endpoints:

One-year cardiovascular mortality

Cardiovascular mortality occurred in 17 (4.7%) patients of the Zofenopril group vs 11 (3.1%) patients in the Ramipril group (Odds Ratio 1.510 [0.697 ; 3.271] p = 0.293): time to event is reported on Figure 2.

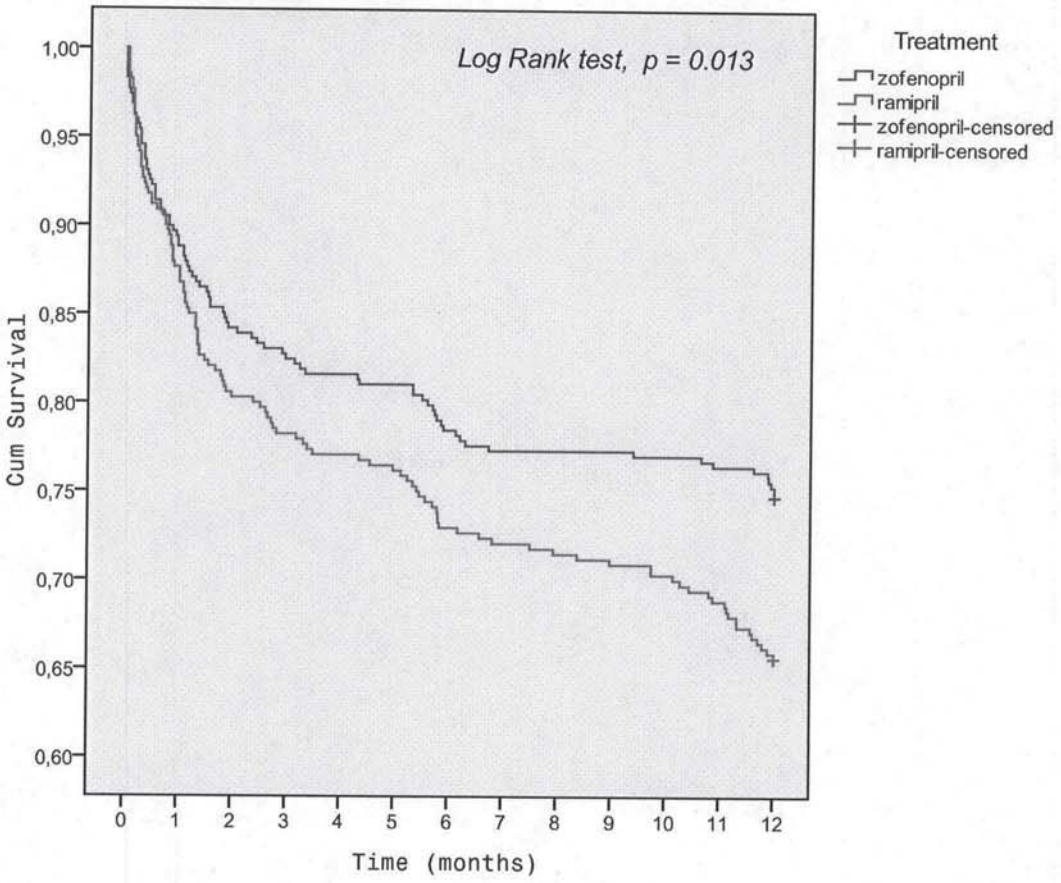
Figure 2. Time to event; One-year mortality for CV cause – Kaplan Meier plot (FAS).



One-year hospitalization for CV causes

Hospitalisation for CV causes occurred in 88 (24.1%) patients of the Zofenopril group vs 117 (33.3%) patients in the Ramipril group (Odds Ratio 0.645 [0.464 ; 0.897] p = 0.009), time to event is reported on Figure 3.

Figure 3. Time to event; One-year Hospitalisation for CV causes – Kaplan Meier plot (FAS).



Changes in LV ejection fraction, LV end-diastolic and end-systolic volumes, plasma NT-proBNP levels analysis.

For **LV Ejection Fraction**, a highly significant change from baseline is obtained in both groups at each visit ($p < 0.0001$) which reaches respectively 5.80 and 4.99 % in the Zofenopril and Ramipril groups at visit 5 ($p = 0.36$).

LV end-diastolic and **end-systolic volumes**: the analysis did not show significant difference between treatments for both parameters.

A highly significant decrease in **NT- proBNP** levels is observed in both groups.

Safety:

A total of 203 patients (52%) in the Zofenopril group and of 196 patients (52%) in the Ramipril group reported at least one treatment-emergent adverse event. Of these, 150 (39%) and 135 (36%) were not related to the cardiovascular system.
Thirty-three patients (9%) in the Zofenopril group and 21 patients (6%) in the Ramipril group reported at least one adverse event related to ACE-I study medication (i.e. classified by the investigator as certainly, probably or possibly related).
Respectively 114 (29 %) in the Zofenopril group and 120 (32%) in the Ramipril group reported at least one serious adverse event; but only 5 (1.3%) in the Zofenopril group and 2 (0.5%) in the Ramipril group were considered as related to ACE-I study treatment.
29 patients (7%) of the Zofenopril group and 18 (5%) of the Ramipril group withdrew due to safety reasons, a minority of them (25 (6%) for Zofenopril and 12 (3%) for Ramipril) for an ACE-I related TEAE.
As detailed in the SAP the Patients with a LVEF decrement (Visit 5 or Visit 4 or Visit 3 – Visit 2 / Visit 2 * 100) percentage ≥15% have been considered in the statistical analysis as event "CV Hospitalization". The number (%) of patients with a LVEF decrement ≥ 15 % in the Zofenopril group is 23 (5.9%) and the number (%) of patients with a LVEF decrement ≥ 15 % in the Ramipril group is 36 (9.5%).

For most of the TEAEs relationship to ACE-I study medication was considered as not related.

The most common treatment-emergent AE events, i.e. events that occurred in more than 1%, were cardiac disorders, the far most common events in both groups followed by vascular disorders: angina pectoris, coronary angioplasty, hypertension, acute myocardial infarction and Coronary Angiography were the TEAEs that occurred in more than 5% of the Zofenopril group: no relevant imbalance is shown between treatment groups respect to these AEs occurrence.

Most of treatment-emergent adverse events were mild to moderate, and resolved during the study.

Eighteen patients (5%) died during the treatment phase in the Zofenopril group and twelve patients (3%) in the Ramipril one (one death not due to CV reasons).

Relationship was considered not related in all cases.

Among serious treatment-emergent adverse events, the most frequent were related to cardiovascular illnesses or concerned surgical and medical procedures: 7 patients reported at least one SAE considered as certainly, probably or possibly related to study ACE-I treatments, 5 of which in the Zofenopril group. These generally occurred in no more than 1 patient with the exception of hypotension, reported by 3 patients in the Zofenopril group.

Two hundred and three reported SAEs occurred during the study (brief narratives are provided); they included 30 cases of death.

CONCLUSIONS:

Efficacy

Two populations were defined for the analysis of efficacy data: the FAS (Full Analysis Set) population and the PP (per protocol) population and the same analysis were carried out for both.

FAS population: the difference in the event rate is -7.7% in favour of Zofenopril. In the Logistic Regression model the prognostic factors LVEF, Killip Class, Revascularization, Type of Infarction and Low HDL show a statistical significant influence on the results ($p < 0.05$). Treatment effect is statistically significant ($p < 0.05$). Time to event was analysed using a Cox Proportional Hazard Model with a stepwise selection of the relevant covariates: again treatment effect was found to be significant ($p < 0.05$) with a Hazard Ratio = 0.758 (95% IC = 0.580 – 0.991). Event-free Survival time, displayed by means of a Kaplan-Meier Analysis, shows a significant difference (Log Rank test, $p<0.05$) in favour of Zofenopril.

PP population: analysis performed on 594 patients lead to a similar result obtained from the analysis performed on FAS population. In this sub-set population the Treatment effect is not statistically significant ($p = 0.122$).

As regards to the secondary endpoints: one-year cardiovascular mortality and one-year hospitalization for CV cause statistical analysis show that difference in CV mortality between Zofenopril and Ramipril groups is not statistically significant ($p = 0.293$).

Hospitalisation for CV causes occurred in 88 (24.1%) patients of the Zofenopril group vs 117 (33.3%) patients in the Ramipril group, the Odds Ratio is equal to 0.645 (95% CI =0.464; 0.897), with a p-value = 0.009. The difference in hospitalization for CV causes is 9.2% in favour of Zofenopril.

For changes in LV ejection fraction, LV end-diastolic and end-systolic volumes, plasma NT-proBNP levels, for LV ejection fraction a highly significant change from baseline is obtained in both groups at each visit ($p < 0.001$); for LV end-systolic volumes and LV end-diastolic volumes in both groups there are no significant difference between treatment for these parameters. A highly significant decrease in NT-proBNP levels is obtained in both groups.

Safety

Considering Safety population (Safety set) the incidence of

- patients with at least 1 treatment-emergent adverse events
- patients with at least one non CV event
- Serious TEAE
- Fatal TEAE
- patients withdrawn due to AE

the incidence and typology of events in the Zofenopril and Ramipril treatment groups are similar.

As regards to clinical laboratory evaluations, no impairment in term of an increase in the proportion of abnormal values was noted the treatments groups. As regards to vital signs, physical findings and other observations related to safety, a progressive significant increase in systolic blood pressure (SBP) is observed in both groups, even if the difference between groups never reaches statistical significance ($p=0.17$). An increase is also obtained for diastolic blood pressure (DBP), whereas heart rate decreases during treatment in both groups; no significant difference between groups is neither observed for these two latter parameters. Difference between groups was not significant for any of the quantitative ECG parameters. Occurrence profile of severe hypotension is similar in both treatment groups. Abnormalities reported during physical examination at the end of the study concerned mainly respiratory and cardiovascular systems and were equally distributed between treatment groups.

The safety profile of Zofenopril and Ramipril seems to be quite similar.

The results of this study demonstrate that Zofenopril in association with ASA 100 mg/day is superior to Ramipril in association with ASA 100 mg/day in the prevention of cardiovascular mortality and morbidity in patients with systolic left ventricular dysfunction after acute myocardial infarction.

The primary efficacy endpoint of this study was the one year mortality and hospitalization for cardiovascular causes: in the FAS population the event rate was 28.8% in the Zofenopril treatment group versus 36.5 % in Ramipril treatment group leading to a statistically significant difference in the event rate of -7.7% in favour of Zofenopril. Similar results were obtained in the per protocol population.

As regards to the secondary endpoints the statistical analysis show that difference in cardiovascular mortality between Zofenopril and Ramipril groups is not statistically significant, while a statistically significance was found in hospitalization for cardiovascular causes with a difference of 9.2% in favour of Zofenopril.

Moreover a highly significant change from baseline was obtained in both groups in left ventricular ejection fraction, left ventricular end-diastolic and end-systolic volumes and plasma NT-proBNP levels without significant differences between treatment.

The safety profile of the two drugs was good: the two treatment group showed a similar incidence of adverse events, serious adverse events, withdrawn rate due to adverse event and no impairment in term of an increase in the proportion of abnormal laboratory values was noted. As regards to other observations related to safety, a progressive significant increase in systolic blood pressure was observed in both groups; an increase for diastolic blood pressure and heart rate decreases were obtained and difference between groups was not significant for any of the quantitative ECG parameters. Occurrence profile of severe hypotension is similar in both treatment groups. Abnormalities reported during physical examination at the end of the study were equally distributed between treatment groups.

From a clinical and statistical point of view the efficacy profile of Zofenopril in association with ASA showed in this study allows to conclude that Zofenopril effects in prevention of cardiovascular mortality and morbidity are superior to those of Ramipril and that Zofenopril can be considered a valuable drug in the treatment of systolic left ventricular dysfunction after acute myocardial infarction.