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

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

1 SYNOPSIS

Title of Study: A multi-center, double-blind, randomized 2x2 factorial design study to compare the efficacy of early (<6 hours) versus late (24-48 hours) ACE-inhibition and to compare the efficacy of Zofenopril and Lisinopril on oxidative reperfusion injury after a first acute myocardial infarction: the ZAAMIS (Zofenopril After Acute Myocardial Infarction Study).

Principal Investigator: [redacted]

Co investigators: [redacted]

Study centres: [redacted]

Publication (reference): n.a.

Studied period (years): 2005-2007 (**date of first enrolment**) March 17, 2005 (**date of last completed**) June 21, 2007	**Phase of development:** IV

Objectives:
To compare the effects of Zofenopril and Lisinopril on oxidative stress as measured by peak urinary concentrations of malonyldialdehyde.
Primary end-point: Peak urine concentrations of Malonyl di-aldehyde.
Secondary endpoints: Neurohormonal parameters

Furthermore echo cardiographic measurements will be made to compare the efficacy of zofenopril and lisinopril on left ventricular function and remodeling and the difference between early (<6 hours after first signs of infarction) and late (>24 and <48 hours) treatment with ACE inhibitors on left ventricular function and remodeling.

Methodology: Randomized, double-blind, two parallel groups study

Number of subjects (planned and analyzed):
- planned for completion: 60
- enrolled and randomized: 43
- withdrawals: 19
- ITT population 43
- completed as per protocol: 24

Main criteria for inclusion:
- Subjects undergoing a primary percutaneous coronary intervention (PCI) for a first acute myocardial infarction.
- Subjects between 18 and 75 years of age (inclusive)
- Written informed consent for participation in the study.

Main criteria for exclusion:
- Significant cardiac valve disease
- Significant rhythm disorders
- Use of ACE-inhibitors prior to myocardial infarction
- Use of Angiotensin receptor blockers prior to myocardial infarction
- Risk on serious depression of hemodynamics due to vasodilatation
- Serum creatinine > 177 mmol/l
- Hemodialysis
- ASAT or ALAT > 3 times upper limit
- Potassium levels > 5.0 mmol/l
- Pregnancy
- Fertile female, unless adequately protected with contraceptives
- Breast-feeding
- Known intolerance to ACE-inhibitors

- Cardiogenic shock (Killip class 4)
- Systolic BP < 100 mmHg
- History of congestive heart failure
- History of angio-edema
- Bilateral renal artery stenoses, or unilateral renal artery stenoses in 1 kidney subjects
- Subjects treated with antidiabetics, NSAID's, lithium, potassium saving diuretics, potassium supplements
- Subjects treated with high doses of diuretics within 24 hrs prior to hospitalization
- Diabetes mellitus
- Aortastenosis
- Any other medical condition that may interfere with the objective of the study according to the opinion of the Investigator.

Test product, dose and mode of administration, batch number:

Test drug 1	: Zofenopril
Formulation	: encapsulated tablets
Strength	: 7.5 and 15 mg
Batch number	: TFE0608
Expiry date	: December 2008
Dose regimen	: from 7.5 b.i.d. to 2 times 15 mg b.i.d.

Duration of treatment: 6 months

Reference product, dose and mode of administration, batch number:

Reference drug 1	: Lisinopril
Formulation	: encapsulated tablets
Strength	: 2.5 and 5 mg
Batch number	: TFE0618
Expiry date	: August 2009
Dose regimen	: from 2.5 mg o.d. to 2 times 5 mg o.d.
Reference drug 2	: Placebo
Formulation	: matching capsules
Strength	: 0 mg
Batch number	: TFE0615
Expiry date	: April 2009
Dose regimen	: from one to 2 tablets per once per day

Criteria for evaluation:

Efficacy: Excretion of Malonyl di-aldehyde from 0-24 hours after PCI and left ventricular ejection fraction before PCI versus ejection fraction 6 weeks after PCI.

Statistical methods:

Data were analyzed in SAS (version 8.2).

Quantitative data were tested using Students' t-test or –if applicable analysis of variance (ANOVA). Semi-quantitative data were tested using Cochran-Mantel-Haenszel test (CMH). Qualitative data and dichotomies were tested using the $\chi 2$ test or Fishers exact probability test. All tests were performed at $\alpha=0.05$ (two-tailed). No correction for multiple testing was applied.

RESULTS

EFFICACY RESULTS:

No statistically significant differences between early administration of Zofenopril, early administration of Lisinopril and late administration of either Zofenopril or Lisinopril were found with regards to urinary Malonyl dia-aldehyde excretion and echographic remodeling parameters.

TOLERABILITY RESULTS:

During the treatment with Zofenopril 16 adverse events AEs were recorded. One out of these 16 AEs was classified as a serious AE (SAE). During the treatment with Lisinopril 25 AEs were recorded. Seven patients treated with Lisinopril suffered from 11 SAEs. Adverse events by severity, causality and outcome are listed in Table 18. Details on AEs are further reported in Appendix 13.10.

CONCLUSION:

Conclusion from this study is that early administration of Zofenopril in patients admitted to the hospital with myocardial infarction does not influence Malonyl di-aldehyde excretion in urine in the 24 hours after PCI was performed, neither does it influence remodeling, as evidenced by ejection fraction, fractional shortening and wall motion index.