# SUMMARY OF CLINICAL STUDY REPORT

## TITLE

**Safety of an ACE-I/CCB fixed combination (Lercanidipine+Enalapril) in elderly hypertensive patients not adequately controlled by CCB monotherapy**

Final version: October 2012

Test drug: lercanidipine and enalapril fixed combination

Indication: Essential hypertension

Study code: REC15/2375–IT–CL 0332 (EUDRACT No.: 2010-019524-31)

Study phase: IIIb

Study design: single-blind, not controlled, multicenter clinical trial in elderly patients

Study initiation date (First patient enrolled): 08 Sep 2010

Study completion date: (Last patient completed): 29 September 2011

Sponsor: Recordati S.p.A; Via Matteo Civitali, 1, 20148 Milan, Italy
Medical Director: Cristina Ghezzi, MD
Clinical Project Leader: Barbara Bettini, MD
Phone No.: +39 02 48787 122/ 480 / Fax No.: +39 02 48787668

CRO: CROMSOURCE, Via Scuderlando, 10 - 37135 Verona, Italy

Study Coordinator: Prof. S. Taddei,
Centro Interdipartimentale di Ricerche di Farmacologia Clinica e Terapia Sperimentale, University of Pisa, Italy

This study was performed in compliance with ICH harmonized tripartite guidelines for good clinical practice (GCP)

| NAME OF SPONSOR/COMPANY:<br>Recordati S.p.A.<br>Milan, ITALY | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|
| NAME OF FINISHED PRODUCT:<br>None<br>NAME OF ACTIVE INGREDIENT(S):<br>Lercanidipine hydrochloride<br>Enalapril maleate | | |

**Protocol No.:** REC 15/2375–IT–CL 0332 (EUDRACT No. 2010-019524-31)

**Title of Study:** Safety of an ACE-I/CCB fixed combination (Lercanidipine+Enalapril) in elderly hypertensive patients not adequately controlled by CCB monotherapy

**Investigators:** See in attachment for the full list of investigators.

**Study Centre(s):** See in attachment This study was performed in 5 sites located in Italy.

**Publication (Reference):** None to date.

| **Studied Period (years):** 08 September 2010 - 29 September 2011<br>[first subject in - last subject visit/procedure] | **Phase of development:** IIIb |
|---|---|

**Objectives:** The primary objective was to collect safety data in elderly patients requiring combination therapy with a fixed dose combination of ACE–I/CCB (Lercanidipine/Enalapril) to improve their blood pressure control.

**Methodology:** This was a single-blind, single-arm, multicenter clinical trial in elderly patients with essential hypertension. The study consisted of 2 periods:

- A 2-week (± 3 days) single-blind placebo run-in period to confirm the inadequate blood pressure control during treatment with the current CCB therapy;
- A 16-week (± 3 days) single-blind active treatment period during which patients received combination therapy with L10mg/E10mg, with a flexible titration to L10mg/E20mg if BP was still ≥ 140/90 mmHg after 8 weeks of therapy (if not otherwise contraindicated for safety reasons according to the investigator's judgment).

Six visits at the clinic were carried out: at screening (start of the run-in period), at baseline (end of run-in/start of combination therapy), and after 4, 8, 12 and 16 weeks of treatment.

**Number of Subjects (planned and analyzed):** Expected enrollment was 100 patients, however this target was not reached up to 31 December 2011 when the enrollment was closed. A total of 42 patients received combination therapy and were analyzed.

**Diagnosis and Main Criteria for Inclusion:** Men or post-menopausal women that expressed their willing to participate in the study by signing the informed consent; subject aged 65-85 years; medical history of essential hypertension not controlled by current CCB monotherapy; mean sitting SBP ≥ 140 mmHg and/or sitting DBP ≥ 90 mmHg at screening and after 2 weeks single-blind period; satisfactory compliance to study medication during the run-in period (80-120%); available to return to all scheduled visits and to comply with protocol requirements.

**Test Product, Dose and Mode of Administration, Batch No.:** L10mg/E10mg or L10mg/E20mg fixed dose combination tablets to be taken once daily in the morning. Batch numbers received by specific subjects are listed in Appendix 16.1.6. L10 mg/E10 mg was provided in batch No. M09D28 and CC0G52. L10 mg/E20 mg was provided in batch No. M09E41 and CE0K90.

**Duration of Treatment:** After 2 weeks of single-blind therapy with placebo (on top of the current CCB medication), patients who met the selection criteria were assigned to 16 weeks of single-blind combination therapy with L10mg/E10mg; a flexible titration to L10mg/E20mg was foreseen after 8 weeks of therapy if BP was still ≥ 140/90 mmHg.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Not applicable.

| NAME OF SPONSOR/COMPANY:<br>Recordati S.p.A.<br>Milan, ITALY | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|
| NAME OF FINISHED PRODUCT:<br>None<br>NAME OF ACTIVE INGREDIENT(S):<br>Lercanidipine hydrochloride<br>Enalapril maleate | | |

**Criteria for Evaluation:**

Efficacy: change from baseline in sitting systolic blood pressure (SSBP) and sitting diastolic blood pressure (SDBP) at trough (24 hours post-dose); responder rate (SSBP < 140 mmHg or decrease from baseline ≥ 20 mmHg) and normalization rate (BP < 140/90 mmHg).

Safety: adverse events (AE), orthostatic test (2-3 hours post-dose after the first intake and 24 hours post-dose at the following visits), heart rate, electrocardiogram (ECG). The following parameters were evaluated in a centralized laboratory: total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglycerides (TG), fasting plasma glucose (FPG), insulin levels, insulin resistance and serum creatinine. Haematology, liver function tests, uric acid, urea, electrolytes and urinalysis were analysed in the local laboratories.

**Statistical Methods:**

Analysis populations: ITT: defined as all patients receiving at least one dose of combination therapy and who had at least one baseline (visit 2) and post-baseline value. Safety population: defined as all patients receiving at least one dose of combination therapy.

Descriptive statistics was provided in summary tables for any variable. Continuous variables were summarized by using number of observations, mean, standard deviation, minimum, median and maximum value. Categorical variables were summarized by using frequency distributions and percentages.

The results of SSBP and SDBP at trough were presented using descriptive statistics at each visit and at end-point. The change from baseline and its 95% confidence interval (CI) was calculated and tabulated at any time point. The number and percent of responder, normalised and patients with a positive orthostatic test and its 95% CI was calculated by dose group (patients with/without titration) and overall at each visit and at any post-baseline time point.

The number of patients with treatment-emergent adverse events (TEAEs) was summarized overall and by dose of combination therapy by SOC and PT using the MedDRA dictionary (version 13.0). Heart rate and difference between sitting and standing BP was presented using descriptive statistics by dose group (patients with/without titration) and overall at each visit and at endpoint. The change from baseline and its 95% CI was calculated and tabulated at any time point. The clinical significance of the laboratory data and ECG was summarized by means of shift tables. Laboratory data evaluated in the centralized laboratory were also summarized by visit in terms of descriptive statistics, mean changes from screening and its 95% CI.

**SUMMARY – CONCLUSIONS**

**Disposition of patients**

A total of 42 patients were administered L10mg/E10mg; 14 of them required titration to L10mg/E20mg. Thirty-nine patients (93%) completed the study, while 3 patients (7%) prematurely discontinued the study (1 patient due to adverse events and 2 patients because lost to follow-up).

**Demographic and baseline characteristics**

Patients in the safety population were divided among males (43%) and females (57%), and all of them were Caucasian. The mean (SD) age was 71.1 (4.3) years, with 76% of patients aged < 75 years. Overall, the mean (SD) screening office SSBP was 155.0 (6.4) mmHg and SDBP was 91.4 (5.1) mmHg. Baseline values were 154.4 (6.6) and 91.5 (3.9) mmHg, respectively.

| NAME OF SPONSOR/COMPANY:<br>Recordati S.p.A.<br>Milan, ITALY | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|
| NAME OF FINISHED PRODUCT:<br>None<br>NAME OF ACTIVE INGREDIENT(S):<br>Lercanidipine hydrochloride<br>Enalapril maleate | | |

**Efficacy results**

A decrease from baseline in office sitting systolic blood pressure (SSBP) and sitting diastolic blood **pressure** (SDBP) at trough was observed all visits. The mean (± SD) change from baseline in SSBP/SDBP at week 16 was -16.4 (11.6) for SSBP and -12.6 (10.1) mmHg for SDBP. Overall, 56% of patients at week 4 and 82% at week 16 were normalized. Eleven out of the 14 patients undergoing titration (78.6%) were normalized at study end. Efficacy results in the ITT population are summarized in the following table. Data measured after the first intake of combination therapy at 2-3 hours post-dose are also reported.

**Change from Baseline in SSBP and SDBP (mmHg) and responder rates**

| | **Baseline (pre-dose)** | **Change from baseline** | | | | |
|---|---|---|---|---|---|---|
| | | **First dose (2-3 hrs post-dose)** | **Week 4 (at trough)** | **Week 8 (at trough)** | **Week 12 (at trough)** | **Week 16 (at trough)** |
| No. of patients | 42 | 42 | 39 | 39 | 39 | 39 |
| **SSBP** | | | | | | |
| Mean ± SD | 154.4 ± 6.6 | -8.7 ± 9.6 | -9.1 ± 8.1 | -11.4 ± 8.6 | -15.5 ± 11.0 | -16.4 ± 11.6 |
| Median | 153.5 | -6.3 | -8.0 | -12.0 | -18.0 | -18.8 |
| 95% CI | | -11.7; -5.7 | -11.6; -6.6 | -14.1;- 8.8 | -19.0; -12.1 | -20.0;-12.8 |
| **SDBP** | | | | | | |
| Mean ± SD | 91.5 ±3.9 | -3.9±5.5 | -4.8 ±5.7 | -8.5±8.7 | -11.2±8.3 | -12.6±10.1 |
| Median | 92.3 | 2.5 | /-3.8 | -7.3 | -10.7 | -11.7 |
| 95% CI | | -5.6;-2.2 | 6.6; -3.0 | - 11.2 ;-5.8 | -13.8; -8.6 | -15.8; -9.4 |
| **Responder** (%) | | 16.7% | 16.7% | 56.4% | 82.1% | 82.1% |
| **Normalized** (%) | | 14.3% | 11.9% | 56.4% | 82.1% | 82.1% |

**Safety results**

- Both dosages of fixed combination lercanidipine/enalapril were well tolerated and no clinically meaningful safety issue was raised during the study.
- 1/42 patients (2.4%) experienced a TEAE (cough) during exposure to L10mg/E10mg, which was considered treatment related and led to early study discontinuation. No SAE was reported.
- The mean difference between sitting and standing blood pressure did not change from baseline to any post-baseline time points. Only one patient had a positive orthostatic test 2-3 hours after the first dose because of an asymptomatic decrease in SBP upon standing > 20 mmHg. However, the test was not positive at the following visits and the patient could safety undergo titration.
- Mean heart rate did not change from baseline, irrespective of dose titration and there were no clinically significant abnormalities in ECG and physical examination in any patient.
- The mean FPG, insulin levels and insulin resistance (HOMA index) did not change from baseline to week 8 and week 16. Similarly there was no unfavourable change in TC, LDL-C and HDL-C and TG. The mean serum creatinine levels also remained unchanged from baseline to endpoint.
- No clinically significant changes were observed in standard laboratory tests performed locally.

**Conclusions:**

| NAME OF SPONSOR/COMPANY:<br>Recordati S.p.A.<br>Milan, ITALY | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|
| NAME OF FINISHED PRODUCT:<br>None<br>NAME OF ACTIVE INGREDIENT(S):<br>Lercanidipine hydrochloride<br>Enalapril maleate | | |

- Treatment with lercanidipine/enalapril fixed combination given for 16 weeks at a starting dose of L10mg/E10mg/day (with possible up titration to L10mg/E20mg/day after 8 weeks) was well tolerated in terms of general and cardiovascular adverse events. There was no evidence of worsening in renal function or metabolic profile at any dose level;
- The decrease from baseline in mean sitting SBP and DBP at trough was marked and sustained up to the end of the 16-week treatment period, with high normalization rates at study end.
- No definitive conclusions can be drawn by this small, uncontrolled study, however the available evidence show that combination therapy with lercanidipine and enalapril could be a safe and effective therapeutic option in elderly patients not well controlled by the current CCB monotherapy:

**Date of the report:** October 2012

# Attachement n.1

## Sites' List

| Investigator | Site |
|---|---|
| Prof. Stefano Taddei | Dipartimento di Medicina Interna, Università degli studi di Pisa, Ospedale Santa Chiara - Via Roma 67, Edificio n.8, 1° piano, 56126 Pisa |
| Prof. Gianfranco Parati | IRCCS Istituto Auxologico Italiano, Ospedale S.Luca, Centro dell'Ipertensione Piazzale 20, 20149 Milano |
| Prof. Claudio Ferri | Dipartimento Medicina Interna e Sanità Pubblica Divisione di Medicina Interna Universitaria I, Ospedale San Salvatore - Via Vetoio 1, 67100 Coppito (L'Aquila) |
| Prof. Enrico Agabiti Rosei | Clinica Medica Seconda Medicina, Spedali Civili di Brescia Piazza Spedali Civili 1, 25100 Brescia |
| Dr. Roberto Meazza | Centro Ipertensione, Medicina Cardiovascolare, Università di Milano, Ospedale Maggiore Policlinico - Via Sforza 35, 20122 Milano |