These Clinical Trial Results are provided for informational purposes only.

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2. SYNOPSIS

Name of Sponsor: Daiichi Sankyo Europe GmbH Name of Finished Product: CS-866 Name of Active Ingredient: Olmesartan medoxomil	Individual Trial Table Referring to Part <<insert part #>> of the Dossier Volume: Page:	(For National Authority Use only)

Title of Study: A 24-week multicentre, randomised, double blind, controlled, parallel group non-inferiority study to assess the efficacy and safety of olmesartan medoxomil versus candesartan cilexetil in patients with symptomatic heart failure (New York Heart Association NYHA II-IV) (Protocol DSE-866-45; EudraCT Number 2007-003060-22)

Investigators: [redacted]

Study Centre(s): A total of 30 investigative sites screened patients in Europe (3 in Czech Republic, 6 in France, 8 in Germany, 8 in The Netherlands and 5 in Poland).

Publication (reference): None

Study Period:	**Phase of Development**:
First patient in: 18 June 2008 Last patient out: 12 November 2009	Phase IIIb

Objectives:

The primary objective was to demonstrate the non-inferiority of olmesartan medoxomil versus candesartan cilexetil in reducing B-type (or brain) natriuretic peptide (BNP), a prognostic biomarker of heart failure, at week 24 (including the up-titration phase).

The secondary objectives were:

- To assess changes in BNP at week 4, 8, 16 and 24,
- To assess proportion of BNP responders at week 4, 8, 16 and 24 (BNP levels reduced to 350 pg/ml or less at all time points),
- To assess cardiovascular events and deaths occurring within 24 weeks of treatment,
- To assess change in clinical status (improvement, no change, worsening).

Safety and tolerability of the treatment regimen was assessed in terms of treatment emergent adverse events (TEAEs), physical examination, vital signs, electrocardiogram (ECG) and laboratory parameters.

Trial Hypotheses:

It was hypothesised that the addition to conventional therapy of olmesartan medoxomil 10-80 milligrams per day (mg/d) would have an effect on serum BNP, which would be non-inferior to that of candesartan cilexetil 4-32 mg daily.

The hypothesis of inferiority would be rejected - and that of non-inferiority accepted - if the lower bound of the two-sided 95% confidence interval (CI) of the difference between the effects of olmesartan medoxomil and candesartan cilexetil on BNP was greater than 75 pg/ml.

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Methodology:

This phase IIIb trial was a randomised, controlled, double blind, multicentre, non-inferiority trial conducted in 30 investigational sites in Europe. Patients with symptomatic, clinically stable chronic heart failure (CHF) with left ventricular systolic dysfunction (NYHA class II-IV and left ventricular ejection fraction (LVEF) < 40%) and elevated BNP levels (BNP > 400 pg/ml or NT-ProBNP levels > 1500 pg/ml), were randomised in two parallel groups (olmesartan medoxomil or candesartan cilexetil) with a ratio of 1:1.

After screening, eligible patients, including patients who were on stable conventional treatment with diuretics, angiotensin converting enzyme (ACE) inhibitors and/or beta-blockers and/or aldosterone antagonists for at least 2 months prior to randomisation for all ongoing medications, had to proceed immediately and not later than 2 weeks after the screening visit, to the randomisation visit. In addition, patients with beta-blocker therapy had to have been initiated on beta-blockers more than 3 months before randomisation. The screening period could last a maximum of 2 weeks. During this period the patients remained on their usual treatment.

The first dose of study drug had to be administered immediately after randomisation (T1): 10 mg once daily (OD) of olmesartan medoxomil or 4 mg OD of candesartan cilexetil. The investigators doubled the dose, at visits scheduled every 2 weeks (T2 to T4), unless the patient exhibited symptoms of intolerance (symptomatic hypotension, serum creatinine increase and/or potassium increase) or the target dose level (candesartan cilexetil: 32 mg OD, olmesartan medoxomil: 80 mg OD) was reached.

Duration of Treatment:

The treatment duration was planned to be 24 weeks: 8 weeks randomised active treatment titration period and 16 weeks randomised active treatment maintenance period.

Number of Patients:

Planned: 400 patients

Screened: 114 patients

Enrolled/Randomised: 71 patients (36 to olmesartan medoxomil and 35 to candesartan cilexetil)

Completed: 17 (23.9%) patients (6 [16.7%] in the olmesartan medoxomil group and 11 [31.4%] in the candesartan cilexetil group)

Discontinued: 54 (76.1%) patients, 42 (59.2%) of them due to study terminated by Sponsor

Diagnosis and Main Criteria for Inclusion:

Male or female, adult, out-patients aged between 18 and 85 years with symptomatic, clinically stable CHF with left ventricular systolic dysfunction [NYHA class II-IV and LVEF < 40%] and elevated BNP levels (>400 pg/ml or NT-ProBNP levels > 1500 pg/ml).

Investigational Product and Comparator Information:

Dosage Form: olmesartan medoxomil 10, 20 and 40 mg film-coated tablets or candesartan cilexetil 4, 8 mg and 16 mg over-encapsulated tablets, and matching placebos.

Route of Administration: oral, OD.

Lot No.: olmesartan medoxomil 10 mg: [redacted], 20 mg: [redacted], 40 mg; [redacted];

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candesartan cilexetil 4 mg: [redacted] (=12755) and [redacted] (=14424), 8 mg: [redacted] (=13584) and [redacted] (=14740), 16 mg: [redacted] (=13665), 2x16 mg: [redacted] (=13665); matching placebo to olmesartan 10 mg: [redacted], 20 mg: [redacted], 40 mg: [redacted]; matching placebo to candesartan 4 to 2x16 mg: [redacted].

Packaging Information: The products were packaged in double aluminium blisters. One patient kit for the titration phase contained four visit boxes for visit T1 - T4. Four Patient Kits for the titration phase were assembled into one block box. The patient kits for the maintenance phase contained two visit boxes for visit M1 and M2.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was absolute BNP change from week 0 to week 24 of treatment.

The secondary efficacy parameters were:

- Proportion of BNP responders at week 4, 8, 16 and 24.
- BNP change from week 0 to week 4, 8 and 16.
- Other neurohormonal and remodelling biomarker blood levels change from week 0 to week 4, 8, and 16 were planned to be assessed. However, due to the early termination of the study, these parameters were not analysed.
- Incidence of critical events at 24 weeks (all cause death, cardiovascular death, hospitalisation for heart failure worsening, hospitalisation for other cardiovascular reason).
- Event-free survival.
- Time-to-death, where death can be for any cause.
- Time-to-first cardiovascular event.
- Change in clinical status.

Safety:

Safety and tolerability were addressed in terms of occurrences of adverse events (AEs), TEAEs, changes in vital signs (blood pressure/heart rate), ECGs, physical examination findings and laboratory parameters.

Statistical Methods:

No efficacy analyses or summaries were carried out for this study, but efficacy endpoints were listed. BNP levels, BNP responder status and clinical status at each visit were listed. As not all patients had the opportunity to complete the study, for critical event and time to event endpoints, the date that the endpoint was reached and their last week in the study were listed. No other neurohormonal or remodelling biomarker blood levels were analysed.

Comprehensive data summaries were prepared for TEAEs and laboratory parameters. Vital signs and ECG measurements were summarised for the Baseline visit, by treatment group. All vital signs, ECG and physical examination data were listed.

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Summary:

This study was terminated early due to significantly delayed patient enrolment and markedly reduced recruitment rate compared to the original assumptions. For this reason, patients were not analysed by the populations defined in the trial Protocol and only the safety population was analysed.

The safety population included 69 patients (34 in the olmesartan medoxomil group and 35 in the candesartan cilexetil group). Two patients in the olmesartan medoxomil group did not receive study medication and were therefore excluded from the safety population.

The treatment groups were comparable with respect to demographic and baseline characteristics.

Efficacy Results: Due to the early termination of the trial, limited efficacy data were available and no conclusions could be drawn.

Safety Results: During the study 46 (66.7%) patients experienced at least one TEAE during the study, of whom 28 (40.6%) patients experienced at least one drug-related (definite, probable, possible or missing relationship) TEAE. The frequency of TEAEs was similar between the treatment groups: 22 (64.7%) and 24 (68.6%) patients with TEAEs in the olmesartan medoxomil group and the candesartan cilexetil group, respectively. The frequency of drug-related TEAEs was higher in the candesartan cilexetil group than in the olmesartan medoxomil group, with 16 (45.7%) and 12 (35.3%) patients, respectively.

The most common drug-related TEAEs by preferred term were hyperkalaemia and vertigo, with a similar incidence in the olmesartan medoxomil group (5 [14.7%] and 3 [8.8%] patients, respectively) and the candesartan cilexetil group (5 [14.3%] and 4 [11.4%] patients, respectively), and hypotension, with a higher incidence in the olmesartan medoxomil group (5 [14.7%] patients) than in the candesartan cilexetil group (2 [5.7%] patients).

Most of the reported TEAEs were of mild or moderate severity, and only 4 (11.8%) patients in the olmesartan medoxomil group and 1 (2.9%) patient in the candesartan cilexetil group reported severe TEAEs. Of these severe TEAEs, only 1 event of hypotension in the olmesartan medoxomil group was considered to be drug-related.

No deaths were reported during the study. The incidence of treatment emergent SAEs was low. These were reported by 6 (8.7%) patients, 3 patients in each treatment group, with all events considered to be unrelated or unlikely related to study drug.

A total of 18 (26.1%) patients experienced 31 TEAEs leading to discontinuation of study drug, with no differences observed between the treatment groups. In the olmesartan medoxomil group 9 (26.5%) patients experienced 16 TEAEs leading to study drug discontinuation and in the candesartan cilexetil group 9 (25.7%) patients experienced 15 TEAEs leading to study drug discontinuation. The most commonly reported TEAEs leading to study drug discontinuation were hypotension, reported by 4 (11.8%) patients in the olmesartan medoxomil group and 2 (5.7%) patients in the candesartan cilexetil group, and hyperkalaemia, reported by 3 (8.8%) and 1 (2.9%) patients, respectively.

Regarding TEAEs related to the hypotensive effect of the study drugs, dizziness and vertigo, no marked differences were observed between the treatment groups.

Laboratory data, vital signs, physical examination and ECG data did not reveal any safety concern.

Overall, the treatments were safe and well tolerated.

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Conclusions: Due to the early termination of the trial, limited efficacy data were available and no conclusions could be drawn. Safety findings were consistent with the known safety profile of the study drugs and no safety concerns were identified during the study.		
Date of the Report: 07 June 2010		