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2 SYNOPSIS

<table>
<tr><td>Name of Sponsor:
Daiichi Sankyo Europe GmbH</td><td rowspan="3">Individual Trial Table Referring to Part of the Dossier
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Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
CS-8663</td></tr>
<tr><td>Name of Active Ingredient:
olmesartan medoxomil + amlodipine besylate</td></tr>
<tr><td colspan="3">Title of Trial: Add-on Study of Olmesartan Medoxomil in Patients With Moderate to Severe Hypertension not Achieving Target Blood Pressure on Amlodipine 5 mg Alone (CS8663-A-E303) (Results of the Open-Label Treatment Period – Period IV)</td></tr>
<tr><td colspan="3">Investigators: [redacted]</td></tr>
<tr><td colspan="3">Trial Centres: 75 investigative centres in Europe</td></tr>
<tr><td colspan="3">Publication (reference): none</td></tr>
<tr><td colspan="2">Trial Period: 83 weeks
Initiation date: 3 October 2005
Completion date: 8 May 2007</td><td>Phase of Development: III</td></tr>
<tr><td colspan="3">Note: This report provides the final results from Period IV of the study. The results for Periods I to III are provided in the CS8663-A-E303 Clinical Trial Report dated 26 April 2007.

Trial Objectives: The primary objective was to demonstrate the additional antihypertensive efficacy in lowering sitting diastolic blood pressure (DBP) gained by adding olmesartan medoxomil (OM) 10 mg, 20 mg, or 40 mg to the treatment regimen in patients with moderate to severe hypertension not adequately controlled on amlodipine (AML) 5 mg alone assessed by conventional blood pressure (BP) measurements after 8 weeks of double-blind treatment.

Secondary objectives included the following:
• To evaluate after 4 and 8 weeks of double-blind treatment the additional antihypertensive efficacy of various combinations of OM and AML compared to monotherapy with AML 5 mg alone in lowering sitting trough systolic blood pressure (SBP) using conventional BP measurements;
• To evaluate after 4 weeks of double-blind treatment the additional antihypertensive efficacy of various combinations of OM and AML compared to monotherapy with AML 5 mg alone in lowering sitting trough DBP using conventional BP measurements;
• To evaluate after 8 weeks of double-blind treatment the additional antihypertensive efficacy in lowering DBP and SBP using 24-hour ambulatory blood pressure monitoring (ABPM);
• To evaluate the effect of titration to various dose combinations of OM and AML on DBP and SBP using conventional BP measurements and 24-hour ABPM;</td></tr>
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- To evaluate the number (%) of patients in each treatment group achieving BP goal (DBP <90 mmHg and SBP <140 mmHg for nondiabetic patients, and DBP <80 mmHg and SBP <130 mmHg for diabetic patients) after 8 weeks of double-blind treatment and after the additional 8-week up-titration period as assessed by conventional BP measurements;
- To evaluate the safety and tolerability of various combinations of OM and AML versus AML 5 mg monotherapy after 8 weeks of double-blind treatment and after the additional 8-week up-titration period; and
- To evaluate the long-term safety and sustained efficacy of various combinations of OM and AML.

Methodology: This was a 52-week, phase III, randomised, parallel-group, multi-centre, multi-national trial consisting of 4 periods: Period I, an 8-week, open-label treatment period with AML 5 mg monotherapy; Period II, an 8-week, double-blind treatment period with randomisation to a fixed combination of OM and AML; Period III, an 8-week, double-blind treatment period with dose up-titration if needed; and Period IV, a 28-week, open-label, long-term extension period with possible dose titration.

Table S1: Study Design

Study Period	Treatment Groups/Regimens
Period I – Open-Label Monotherapy (Week 0 to Week 8)	AML 5 mg
Period II – Double-Blind Treatment (Week 8 to Week 16)	Nonresponders to AML 5 mg monotherapy were assigned randomly to 1 of 4 treatment groups: Placebo + AML 5 mg OM 10 mg + AML 5 mg OM 20 mg + AML 5 mg OM 40 mg + AML 5 mg
Period III – Double-Blind Treatment With Dose Up-titration (Week 16 to Week 24)	Patients whose BP was inadequately controlled at the end of Period II (mean sitting DBP ≥90 mmHg and mean sitting SBP ≥140 mmHg) underwent dose titration at the beginning of Period III: Placebo + AML 5 mg to OM 20 mg + AML 5 mg OM 10 mg + AML 5 mg to OM 20 mg + AML 5 mg OM 20 mg + AML 5 mg to OM 40 mg + AML 5 mg OM 40 mg + AML 5 mg to OM 40 mg + AML 10 mg All other patients continued on their randomised treatment regimen.
Period IV – Open-Label Combination Therapy (Week 24 to Week 52)	Initial treatment with OM 40 mg + AML 5 mg Then: OM 40 mg + AML 10 mg (if needed) Then: OM 40 mg + AML 10 mg + HCTZ 12.5 mg (if needed) Then: OM 40 mg + AML 10 mg + HCTZ 25 mg (if needed)

AML = amlodipine; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; SBP = systolic blood pressure.

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After 1 to 2 weeks of tapering off previous antihypertensive medication (not applicable for newly diagnosed hypertensive patients or patients who were on AML 5 mg or 10 mg), patients eligible for the study entered an 8-week, open-label, run-in period with AML 5 mg (Period I). Patients who were on AML 5 mg or 10 mg at screening entered directly into Period I with AML 5 mg without tapering off antihypertensive medication.

At the end of Period I, patients who did not respond adequately to AML 5 mg monotherapy (i.e., nonresponders, defined as patients with a mean sitting trough DBP ≥90 mmHg, a mean sitting trough SBP ≥140 mmHg, and a mean 24-hour DBP assessed by ABPM of ≥80 mmHg with at least 30% of daytime DBP readings >85 mmHg) were assigned randomly to double-blind treatment for 8 weeks (Period II) with OM 10 mg, 20 mg, 40 mg, or placebo in addition to AML 5 mg. Patients with a mean sitting trough DBP >115 mmHg or a mean sitting trough SBP >200 mmHg were excluded from further participation. Patients who responded adequately to AML 5 mg monotherapy were discontinued from the study.

At the end of Period II, patients whose BP was not adequately controlled (defined as a mean sitting trough DBP ≥90 mmHg and a mean sitting trough SBP ≥140 mmHg) underwent dose titration during Period III. Patients randomised to combination therapy with OM 10 mg + AML 5 mg, OM 20 mg + AML 5 mg, and OM 40 mg + AML 5 mg had their doses titrated to OM 20 mg + AML 5 mg, OM 40 mg + AML 5 mg, and OM 40 mg + AML 10 mg, respectively. Patients randomised to therapy with placebo + AML 5 mg had their dose titrated to OM 20 mg + AML 5 mg. Patients whose BP was adequately controlled at the end of Period II remained on the same randomised treatment during Period III. Patients and investigators remained blinded to study medication during Period III.

At the end of Period III, patients entered a 28-week, open-label, long-term extension period (Period IV). Patients initially received open-label OM 40 mg + AML 5 mg. If BP was inadequately controlled at this dose (defined as a mean sitting trough DBP ≥90 mmHg and a mean sitting trough SBP ≥140 mmHg), investigators could titrate the doses first to OM 40 mg + AML 10 mg and then to triple therapy with OM 40 mg + AML 10 mg + hydrochlorothiazide (HCTZ) 12.5 mg and if needed to OM 40 mg + AML 10 mg + HCTZ 25 mg.

Sphygmomanometers were used for conventional BP measurements throughout the trial. After a 10-minute rest period, 3 separate sitting BP measurements were taken at least 1 minute apart. The 3 results were averaged and rounded to a whole integer. In addition, 24-hour ABPM was performed 4 times during the study (1 day prior to the start of Periods I, II, III, and IV).

Duration of Treatment: 52 weeks

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Number of Patients:

Planned: 632 randomised patients

Randomised: 755 patients

Entered Period IV: 692 patients

Completed Period IV: 673 patients

Diagnosis and Main Criteria for Inclusion: Patients enrolled in this study were male and female patients ≥18 years of age, with moderate to severe hypertension. To enter Period I, newly diagnosed hypertensive patients and patients previously on antihypertensive medications other than AML 5 mg or 10 mg must have had a mean sitting DBP ≥100 mmHg, a mean sitting SBP ≥160 mmHg, and a mean 24-hour DBP assessed by 24-hour ABPM of ≥84 mmHg with at least 30% of daytime DBP readings >90 mmHg. To enter Period I, patients on AML 5 mg or 10 mg monotherapy must have had a mean sitting DBP ≥90 mmHg, a mean sitting SBP ≥140 mmHg, and a mean 24-hour DBP assessed by 24-hour ABPM of ≥80 mmHg with at least 30% of daytime DBP readings >85 mmHg. In addition, patients must have met all other entry qualifications based on medical history, physical examination, electrocardiogram (ECG), and laboratory tests. To be randomised to double-blind combination therapy and enter Period II, patients must have had a mean sitting trough DBP ≥90 mmHg, a mean sitting trough SBP ≥140 mmHg, and a mean 24-hour DBP ≥80 mmHg with at least 30% of daytime DBP readings >85 mmHg.

Investigational Product and Comparator Information:

Investigational Product: OM 10 mg tablets (Lot #[redacted])
OM 20 mg tablets (Lot #[redacted])
OM 40 mg tablets (Lot #[redacted])
AML 5 mg tablets (Lot #[redacted])
AML 10 mg tablets (Lot #[redacted])
HCTZ 12.5 mg tablets (Lot [redacted])

Comparator: OM 10 mg placebo tablets (Lot #[redacted])
OM 20 mg placebo tablets (Lot #[redacted])
OM 40 mg placebo tablets (Lot #[redacted])
AML 5 mg placebo tablets (Lot #[redacted])
AML 10 mg placebo tablets (Lot #[redacted])

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Criteria for Evaluation:

Efficacy: The efficacy parameters evaluated for this report included the following:

- Mean sitting DBP at Weeks 28, 34, 43, and 52, and Week 52/Early Termination;
- Mean sitting SBP at Weeks 28, 34, 43, and 52, and Week 52/Early Termination;
- Mean changes in sitting DBP and SBP during Period IV with titration from one dose regimen to the next;
- The number (%) of patients achieving BP goal (DBP <90 mmHg and SBP <140 mmHg for nondiabetic patients, and DBP <80 mmHg and SBP <130 mmHg for diabetic patients) during Period IV; and
- The number (%) of patients reaching BP thresholds (<120/80 mmHg, <130/80 mmHg, <130/85 mmHg, and <140/90 mmHg) during Period IV.

Safety: Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory test results, vital signs, physical examinations, and 12-lead ECG assessments.

Statistical Methods: Mean sitting DBP and SBP values were summarised at Weeks 28, 34, 43, and 52, and Week 52/Early Termination by treatment regimen for patients who entered Period IV. Descriptive statistics were computed for the titration effect, quantifying the mean change in sitting DBP and SBP when the dose regimen was titrated from OM 40 mg + AML 5 mg to OM 40 mg + AML 10 mg, from OM 40 mg + AML 10 mg to OM 40 mg + AML 10 mg + HCTZ 12.5 mg, and from OM 40 mg + AML 10 mg + HCTZ 12.5 mg to OM 40 mg + AML 10 mg + HCTZ 25 mg.

The number and percentage of patients on each treatment regimen who achieved BP goal during Period IV were tabulated. For this analysis, BP goal was defined as <140/90 mmHg for nondiabetic patients and <130/80 mmHg for diabetic patients. The number and percentage of patients on each treatment regimen who reached predefined BP thresholds were also tabulated.

Summaries of TEAEs and drug-related TEAEs were prepared for Period IV. The numbers and percentages of patients with TEAEs and drug-related TEAEs were tabulated by system organ class and preferred term for each treatment regimen. Serious adverse events (SAEs) and discontinuations due to adverse events were listed according to treatment group and patient. Other safety summaries included changes in safety laboratory parameters, vital signs, ECG data, and physical examination findings.

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Efficacy Results: In total, 692 patients entered the open-label Period IV; 691 patients initially received OM 40 mg + AML 5 mg as specified in the protocol, and 1 patient initially received OM 40 mg + AML 10 mg. For the 452 patients on OM 40 mg + AML 5 mg at Week 52/Early Termination, the mean sitting DBP was 83.1 mmHg and the mean sitting SBP was 131.4 mmHg. For the 144 patients on OM 40 mg + AML 10 mg at Week 52/Early Termination, the mean sitting DBP was 85.4 mmHg and the mean sitting SBP was 135.0 mmHg. For the 68 patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg at Week 52/Early Termination, the mean sitting DBP was 87.3 mmHg and the mean sitting SBP was 138.3 mmHg. For the 27 patients on OM 40 mg + AML 10 mg + HCTZ 25 mg at Week 52/Early Termination, the mean sitting DBP was 89.7 mmHg and the mean sitting SBP was 145.6 mmHg.

Of the 452 patients on OM 40 mg + AML 5 mg at Week 52/Early Termination, 336 (74.3%) reached BP goal. Of the 144 patients on OM 40 mg + AML 10 mg at Week 52/Early Termination, 85 (59.0%) reached BP goal. Of the 68 patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg at Week 52/Early Termination, 32 (47.1%) reached BP goal. Of the 27 patients on OM 40 mg + AML 10 mg + HCTZ 25 mg at Week 52/Early Termination, 9 (33.3%) reached BP goal.

Titration from OM 40 mg + AML 5 mg to OM 40 mg + AML 10 mg during Period IV resulted in a mean reduction in sitting DBP of 5.5 mmHg and a mean reduction in sitting SBP of 8.8 mmHg. Titration from OM 40 mg + AML 10 mg to OM 40 mg + AML 10 mg + HCTZ 12.5 mg resulted in a mean reduction in sitting DBP of 6.3 mmHg and a mean reduction in sitting SBP of 10.2 mmHg. Titration from OM 40 mg + AML 10 mg + HCTZ 12.5 mg to OM 40 mg + AML 10 mg + HCTZ 25 mg resulted in a mean reduction in sitting DBP of 3.7 mmHg and a mean reduction in sitting SBP of 3.8 mmHg.

Of the 691 patients exposed to OM 40 mg + AML 5 mg during Period IV, 517 (74.8%) reached BP goal. Of the 243 patients exposed to OM 40 mg + AML 10 mg, 121 (49.8%) reached BP goal. Of the 93 patients exposed to OM 40 mg + AML 10 mg + HCTZ 12.5 mg, 41 (44.1%) reached BP goal. Of the 28 patients exposed to OM 40 mg + AML 10 mg + HCTZ 25 mg, 9 (32.1%) reached BP goal.

Safety Results: In total, 228 (33.0%) patients on OM 40 mg + AML 5 mg, 60 (24.7%) patients on OM 40 mg + AML 10 mg, 17 (18.3%) patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg, and 7 (25.0%) patients on OM 40 mg + AML 10 mg + HCTZ 25 mg had a TEAE during Period IV. Forty-two (6.1%) patients on OM 40 mg + AML 5 mg, 11 (4.5%) patients on OM 40 mg + AML 10 mg, 3 (3.2%) patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg, and 1 (3.6%) patient on OM 40 mg + AML 10 mg + HCTZ 25 mg had a TEAE that was considered by the investigator to be related (definitely, probably, or possibly) to study treatment. Most of the TEAEs were mild or moderate in severity.

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No patients died during Period IV. Ten (1.4%) patients had an SAE during Period IV: 9 (1.3%) patients on OM 40 mg + AML 5 mg and 1 (0.4%) patient on OM 40 mg + AML 10 mg. None of the SAEs was considered by the investigator to be related to study treatment. Two SAEs led to discontinuation from the study (1 patient with atrial fibrillation and 1 patient with a pulmonary embolism).

Nine (1.3%) patients discontinued from the study during Period IV due to a TEAE: 7 (1.0%) patients on OM 40 mg + AML 5 mg and 2 (0.8%) patients on OM 40 mg + AML 10 mg. For 6 (0.9%) patients on OM 40 mg + AML 5 mg and 1 (0.4%) patient on OM 40 mg + AML 10 mg, the TEAE that led to discontinuation was considered by the investigator to be related to study treatment (3 patients with dizziness, 1 patient with increased alanine aminotransferase, 1 patient with hypotension, 1 patient with face oedema, and 1 patient with dry mouth and nasal dryness).

The incidence rates of hypotension and peripheral oedema during Period IV were low for patients on the various treatment regimens. Five (0.7%) patients on OM 40 mg + AML 5 mg reported an adverse event of hypotension during Period IV. Twelve (1.7%) patients on OM 40 mg + AML 5 mg and 6 (2.5%) patients on OM 40 mg + AML 10 mg reported an adverse event of peripheral oedema during Period IV.

Mean changes in safety laboratory parameters during Period IV were not clinically meaningful for patients on the various treatment regimens. No clinically meaningful safety findings or trends in safety laboratory parameters were noted.

Mean changes in ECG parameters during Period IV were not clinically meaningful. No clinically meaningful differences in pulse rate or ECG parameters were observed among the various treatment regimens. No clinically meaningful physical examination findings were noted.

Conclusions: Long-term treatment with OM + AML demonstrated maintenance of the BP-lowering effects observed in earlier periods of the study. No new safety concerns with combination treatment with OM + AML with the possible addition of HCTZ were identified that were unexpected for these classes of drugs. Overall, the incidence of adverse events was low with all of the evaluated treatment regimens. Long-term treatment with OM + AML or the triple combination of OM + AML + HCTZ was safe and well tolerated.

Date of the Report: Final v1.0 19 November 2007