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2. SYNOPSIS

Name of Sponsor: Daiichi Sankyo Europe GmbH **Name of Finished Product:** CS-8663 **Name of Active Ingredients:** olmesartan medoxomil + amlodipine besylate	**Individual Trial Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Title of Trial: Efficacy and Safety of Amlodipine Used as Add-On Therapy in Moderately to Severely Hypertensive Patients Not Adequately Controlled by Olmesartan Medoxomil 20 mg Monotherapy (CS8663-A-E302)

Investigators: [redacted]

Trial Centres: 47 investigative sites in Europe

Publication (reference): none

Trial Period: 60 weeks **Initiation date:** 28 October 2005 **Completion date:** 22 December 2006	**Phase of Development:** III

Trial Objectives:

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

Secondary Objectives:

Secondary objectives were:

- To evaluate after 4 weeks and 8 weeks of double-blind treatment, the additional antihypertensive efficacy in trough sitting systolic blood pressure (SBP) lowering of the combinations of OM and AML compared to monotherapy with OM 20 mg using conventional BP measurements;
- To evaluate after 4 weeks of double-blind treatment, the additional antihypertensive efficacy in trough sitting DBP lowering of the combinations of OM and AML compared to monotherapy with OM 20 mg using conventional BP measurements;
- To evaluate the additional antihypertensive efficacy in DBP and SBP lowering using 24-hour ambulatory blood pressure monitoring (ABPM) after 8 weeks of double-blind treatment;
- To evaluate the number and percentage of patients in each treatment group achieving BP goal (defined as BP <140/90 mmHg, <130/80 mmHg for diabetic patients) as assessed by conventional BP measurements after 4 weeks and after 8 weeks of double-blind treatment;

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and

- To evaluate the safety and tolerability of the co-administration of OM and AML versus monotherapy with OM 20 mg after 8 weeks of double-blind treatment.

Methodology: This was a multi-centre, multi-national, randomised, double-blind, parallel-group trial consisting of a 1- to 2-week taper-off phase (applicable to eligible patients being treated with antihypertensive medication other than OM 20 mg or OM 40 mg at the time of screening for the trial) and 2 treatment periods (Period I and Period II). Period I (Visit 2 and Visit 3; Day 1 to Week 8) was an 8-week open-label period during which all patients received monotherapy with OM 20 mg. At the end of Period I (Visit 4/Week 8 [randomisation visit]), only non-responders were eligible to be randomised (see Diagnosis and Main Criteria for Inclusion) and enter Period II. Patients whose BP was controlled on OM 20 mg at Week 8 were discontinued from the study. Period II (Visit 4, Visit 5, and Visit 6; Week 8 to Week 16) was an 8-week double-blind period during which patients non-responsive to OM 20 mg treatment during Period I were assigned randomly in a 1:1:1 ratio to 1 of 3 treatment groups:

- OM 20 mg + placebo,
- OM 20 mg + AML 5 mg, or
- OM 20 mg + AML 10 mg.

Patients recruited to participate in the trial had a history of moderate to severe hypertension or were patients with newly diagnosed moderate to severe hypertension. Patients with a history of hypertension were further classified by type of prior antihypertensive treatment (i.e., treated with OM therapy [20 mg or 40 mg] or treated with antihypertensive medications other than OM). See below for trial inclusion criteria regarding BP.

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 3 times during the study (1 day prior to Visits 2, 4, and 6).

Duration of Treatment: 16 weeks (8 weeks of open-label monotherapy and 8 weeks of double-blind treatment)

Number of Patients:

Planned: 429 randomised patients

Screened: 1519 patients

Entered Monotherapy (Period I): 722 patients

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Randomised: 538 patients

Discontinued: 13 patients

Completed: 525 patients

Sample Size: The sample size was calculated based on the following assumptions for Period II: a treatment effect of OM + AML combination therapy versus OM monotherapy in DBP of ≥3 mmHg at the end of 8 weeks of double-blind treatment, a common standard deviation of 7.5 mmHg, 80% power, and an overall Type I error of 0.05. Thus, 121 patients per treatment group were required to complete the study. Assuming a dropout rate of 15%, at least 143 patients were to have been randomised to each treatment group, for a total of 429 patients randomised into the study.

Diagnosis and Main Criteria for Inclusion: Patients enrolled in this study included males and females ≥18 years of age, with a history of moderate to severe hypertension (SBP ≥160 mmHg and DBP ≥100 mmHg). At the screening visit, newly diagnosed hypertensive patients were required to have a mean sitting BP of ≥160/100 mmHg. There were no specific BP requirements at this visit for patients who were required to taper-off their antihypertensive medication (other than OM 20 or 40 mg). Patients being treated with either OM 20 mg or OM 40 mg had to have a previous diagnosis of moderate to severe hypertension and were required to have a mean sitting BP of ≥140/90 mmHg.

The BP requirements for entering the open-label monotherapy treatment period at Visit 2 included a mean sitting BP of ≥160/100 mmHg, a mean 24-hour DBP of ≥84 mmHg, and at least 30% of daytime DBP readings >90 mmHg. Patients treated with either OM 20 mg or OM 40 mg at the beginning of the trial had to have a mean sitting BP of ≥140/90 mmHg, a mean 24-hour DBP of ≥80 mmHg, and at least 30% of daytime DBP readings >85 mmHg.

To enter the double-blind treatment period at Visit 4, patients needed to be non-responders to OM 20 mg. A non-responder was defined as mean trough sitting DBP ≥90 mmHg; mean trough sitting SBP ≥140 mmHg; and mean 24-hour DBP ≥80 mmHg with at least 30% of daytime DBP readings >85 mmHg. In addition to the BP requirements, patients should have met all other entry qualifications based on medical history, physical examination, electrocardiogram (ECG), and laboratory tests.

At any time during the course of the trial, a patient was withdrawn immediately for any of the following reasons:

- Major protocol violations (e.g., pregnancy) if there was a safety risk associated with continuation of the trial;

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- Any change in the patient's condition which in the Investigator's opinion, for reasons of safety or ethics, precluded further participation in the trial;
- Mean sitting DBP >115 mmHg;
- Mean sitting SBP >200 mmHg;
- Mean 24-hour DBP as assessed by 24-hour ABPM >104 mmHg; or
- Bradycardia (<50 beats/min at rest).

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Investigational Product and Comparator Information:

Investigational Product: OM 20 mg tablets (Daiichi Sankyo Batch No. [redacted]
AML 5 mg tablets (Daiichi Sankyo Batch No. [redacted]; Pfizer Lot No. [redacted]
AML 10 mg tablets (Daiichi Sankyo Batch No. 3998V04014; Pfizer Lot No. [redacted]

Comparator: AML 5 mg placebo tablets (Daiichi Sankyo Batch No. [redacted])
AML 10 mg placebo tablets (Daiichi Sankyo Batch No. [redacted])

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the mean change from baseline (Week 8) to Week 16 (end of double-blind treatment period) using last observation carried forward (LOCF) in trough sitting DBP.

The other efficacy variables included the following:

- Mean change from baseline (Week 8) to Week 12 and Week 16 (end of double-blind treatment period) without LOCF in trough sitting DBP;
- Mean change from baseline (Week 8) to Week 12 and Week 16 (end of double-blind treatment period) without LOCF and Week 16 with LOCF in trough sitting SBP;
- Mean change from baseline (Week 8) to Week 16 (end of double-blind treatment period) in daytime, nighttime, and 24-hour DBP and SBP as assessed by 24-hour ABPM; and
- Comparison of the number and percentage of patients who achieved BP goal (DBP <90 mmHg and SBP <140 mmHg for non-diabetic patients; DBP <80 mmHg and SBP <130 mmHg for diabetic patients) after 4 weeks (Week 12) and 8 weeks (Week 16) of double-blind treatment.

Safety: Safety assessments included adverse events, clinical laboratory measurements (hematology, biochemistry, and urinalysis), vital signs, physical examinations, and 12-lead ECG assessments. The primary safety variable was the adverse event profile of the combinations of OM and AML versus OM 20 mg + placebo.

Statistical Methods: The statistical analysis of the primary efficacy parameter was performed on the Full Analysis Set (Intent-to-Treat approach) using the LOCF approach for missing data. The primary analysis was repeated for the Full Analysis Set using the observed case (OC) approach and for the Per-Protocol Set (using OC). Analysis of the primary efficacy parameter was performed using an Analysis of Covariance (ANCOVA) model with treatment and pooled

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centre as effects and baseline DBP as a covariate. Comparisons of the combination therapies (OM 20 mg + AML 5 mg and OM 20 mg + AML 10 mg) versus monotherapy (OM 20 mg + placebo) were made using Dunnett's test to ensure an overall Type I error of 5%.

Analyses for the secondary efficacy parameters were conducted using the statistical model as described above on the Full Analysis Set (LOCF), with supportive analyses utilising the Full Analysis Set (OC) and the Per-Protocol Set. The secondary efficacy parameters concerning the 24-hour ABPM and the conventional BP measurements were analysed using the same ANCOVA model as used for the confirmatory analysis. Analysis of the number and percentage of patients reaching BP goal after 4 and 8 weeks of double-blind treatment was accomplished by means of the Cochran-Mantel-Haenszel test stratified by trial centre. Pooling was applied to small centres randomising a small number of patients (i.e., <10 patients).

The incidence of treatment-emergent adverse events (TEAEs) is provided for both the monotherapy treatment period (Period I) and the double-blind treatment period (Period II). For both treatment periods, TEAEs are summarised by system organ class (SOC) and preferred term. Further, for the double-blind treatment period, summaries are provided by treatment group and in total. Adverse event summaries are similarly provided for treatment-related TEAEs, TEAEs by maximum severity, treatment-emergent serious adverse events (SAEs), and adverse events leading to discontinuation from the trial.

Summary:

Efficacy Results: The primary efficacy analysis demonstrated that 8 weeks of double-blind treatment with the combination of OM + AML (OM 20 mg + AML 5 mg and OM 20 mg + AML 10 mg) reduced mean sitting DBP to a significantly greater extent than treatment with OM 20 mg + placebo. The table below presents the results for mean change and adjusted mean change in sitting DBP from baseline (Week 8) to Week 16 with LOCF for the Full Analysis Set. Treatment with OM + AML combination therapy resulted in statistically significant reductions in adjusted mean sitting DBP when compared with OM 20 mg + placebo therapy: -2.7 mmHg for OM 20 mg + AML 5 mg (p=0.0006) and -3.2 mmHg for OM 20 mg + AML 10 mg (p<0.0001).

Week 16 LOCF Analysis Variable	OM20/Placebo (N = 179)	OM20/AML5 (N = 182)	OM20/AML10 (N = 177)
N [1]	179	182	177
Baseline mean (SD) [2]	97.2 (4.89)	97.5 (4.34)	97.1 (4.22)
Week 16 LOCF mean (SD) [3]	89.4 (8.54)	86.9 (7.39)	86.0 (7.59)
Mean change (SD)	-7.8 (7.86)	-10.6 (7.20)	-11.1 (8.01)
Adjusted mean change (SE) [4]	-7.6 (0.55)	-10.4 (0.55)	-10.9 (0.56)
Treatment comparison with OM20/Placebo			

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Adjusted mean change (SE) [4]		-2.7 (0.75)	-3.2 (0.76)
95% confidence interval [4]		-4.4, -1.1	-4.9, -1.5
P-value [4]		0.0006	<0.0001

1. N = the number of patients with values at both time points.
2. Baseline = Week 8.
3. Week 16 LOCF was defined as the last available measurement during the double-blind treatment period.
4. Statistics were based on an Analysis of Covariance model, including treatment, pooled centre, and baseline value as a covariate. All comparisons are with OM20/Placebo using Dunnett's test to adjust for multiple testing.

AML = amlodipine; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.
Sources: Post-text Tables 14.2.3, 14.2.4, and 14.2.5

Similar results were observed for adjusted mean sitting SBP, and 24-hour BP by ABPM. For mean sitting SBP, the adjusted mean change from baseline (Week 8) to Week 16 with LOCF was -10.2 mmHg for the OM 20 mg + placebo treatment group, -16.1 mmHg for the OM 20 mg + AML 5 mg treatment group, and -16.7 mmHg for the OM 20 mg + AML 10 mg treatment group. Treatment with OM + AML combination therapy resulted in statistically significant reductions in adjusted mean sitting SBP from baseline (Week 8) to Week 16 with LOCF when compared with OM 20 mg + placebo therapy: -5.8 mmHg for OM 20 mg + AML 5 mg ($p<0.0001$) and -6.4 mmHg for OM 20 mg + AML 10 mg ($p<0.0001$).

The adjusted mean change from baseline (Week 8) to Week 16 in 24-hour mean DBP was -4.5 mmHg for the OM 20 mg + placebo treatment group, -7.3 mmHg for the OM 20 mg + AML 5 mg treatment group, and -8.4 mmHg for the OM 20 mg + AML 10 mg treatment group. Treatment with OM + AML combination therapy resulted in statistically significant reductions in 24-hour adjusted mean DBP from baseline (Week 8) to Week 16 LOCF when compared with OM 20 mg + placebo therapy: -2.8 mmHg for OM 20 mg + AML 5 mg ($p=0.0031$) and -3.9 mmHg for OM 20 mg + AML 10 mg ($p<0.0001$).

The adjusted mean change from baseline (Week 8) to Week 16 in 24-hour mean SBP was -6.5 mmHg for the OM 20 mg + placebo treatment group, -11.4 mmHg for the OM 20 mg + AML 5 mg treatment group, and -12.4 mmHg for the OM 20 mg + AML 10 mg treatment group. Treatment with OM + AML combination therapy resulted in statistically significant reductions in 24-hour adjusted mean SBP when compared with OM 20 mg + placebo therapy: -4.9 mmHg for OM 20 mg + AML 5 mg ($p=0.0020$) and -5.8 mmHg for OM 20 mg + AML 10 mg ($p=0.0003$).

Results were similar for mean changes in daytime mean DBP and SBP and nighttime mean DBP and SBP.

The time course of BP reductions demonstrated that in the group of patients that received OM 20 mg + AML 10 mg, earlier reductions in mean sitting DBP and SBP were achieved compared to patients that received OM 20 mg + AML 5 mg. Because of this earlier effect, after 4 weeks of double-blind treatment (Week 12) there was a greater difference between OM 20 mg + AML

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10 mg and OM 20 mg + AML 5 mg compared to the 8 week measurements (Week 16). At the Week 12 visit, the difference in BP reduction between the OM 20 mg + placebo treatment group and the OM + AML combination treatment groups was greater in the OM 20 mg + AML 10 mg treatment group, compared to the OM 20 mg + AML 5 mg treatment group. However, with time, the differences between the 2 combination regimens narrowed and by Week 16, the reductions in BP for both OM + AML combination treatment regimens were very similar.

The greater reductions in BP observed with OM and AML combination treatment translated into significantly more patients achieving pre-defined BP goals in both OM + AML combination treatment groups compared to the OM 20 mg + placebo treatment group. Compared to patients treated with OM 20 mg + placebo (28.5% achieving goal), the percentage of patients achieving BP goal at Week 16 with LOCF was significantly higher in the OM 20 mg + AML 5 mg treatment group (44.5%; p=0.0011) and in the OM 20 mg + AML 10 mg treatment group (45.8%; p=0.0004).

In the subgroup analyses, the efficacy of the OM + AML combination treatment regimens compared to OM 20 mg + placebo was similar for all age groups, for both males and females, and for both categories of hypertension severity.

Safety Results: There were no new safety issues identified during the course of this study with either OM 20 mg + placebo therapy or OM 20 mg and AML 5 mg or 10 mg combination therapy.

A total of 93 (12.9%) patients experienced a TEAE during Period I on OM 20 mg monotherapy, of whom 31 (4.3%) patients experienced a drug-related TEAE. The majority of TEAEs and drug-related TEAEs were considered mild in severity.

A total of 38 (21.2%) patients on OM 20 mg + placebo therapy experienced a TEAE during Period II; 16 (8.9%) of these patients were considered to have had a drug-related TEAE. Thirty-two (17.6%) patients on OM 20 mg + AML 5 mg therapy experienced a TEAE; 14 (7.7%) of these patients were considered to have had a drug-related TEAE. A total of 35 (19.8%) patients on OM 20 mg + AML 10 mg therapy experienced a TEAE; 20 (11.3%) of these patients were considered to have a drug-related TEAE by the Investigator. Across the 3 treatment groups, most TEAEs and drug-related TEAEs were considered mild in severity. The differences in the incidence of TEAEs or drug-related TEAEs were not considered clinically meaningful comparing the OM + AML combination regimens to the OM 20 mg + placebo treatment group.

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For patients in the OM 20 mg + placebo treatment group, the most common SOCs of TEAEs were Investigations (5.0%), Nervous System Disorders (5.0%), Infections and Infestations (3.4%), and Metabolism and Nutrition Disorders (3.4%). For patients in the OM 20 mg + AML 5 mg treatment group, the most common SOCs were Investigations (4.9%), Nervous System Disorders (4.4%), and Cardiac Disorders (3.8%). For patients in the OM 20 mg + AML 10 mg treatment group, the most common SOCs were Investigations (7.9%), Infections and Infestations (4.0%), and Nervous System Disorders (3.4%).

There did not appear to be any meaningful differences in the incidence of adverse events in the OM + AML combination regimens compared to the OM 20 mg + placebo treatment group. Outside of peripheral oedema, which had a slightly higher incidence in the OM 20 mg + AML 10 mg treatment group, there were no clinically meaningful patterns of TEAE incidence that signified that there might be a safety issue in a particular treatment group.

Overall, the most commonly reported drug-related TEAEs in the OM 20 mg + placebo treatment group were headache (1.7%), dizziness (1.1%), and hyperkalaemia (1.1%). The most commonly reported drug-related TEAEs in the OM 20 mg + AML 5 mg treatment group were headache (3.3%), peripheral oedema (1.1%), and hyperkalaemia (1.1%). The most commonly reported drug-related TEAEs in the OM 20 mg + AML 10 mg treatment group were headache (2.3%), peripheral oedema (2.3%), blood potassium increased (1.1%), and gamma-glutamyltransferase (γ-GT) increased (1.1%).

Most drug-related TEAEs reported in this study are well known issues associated with these classes of drugs. Outside of peripheral oedema which appears to have a higher incidence in the OM 20 mg + AML 10 mg treatment group, the differences in the incidence of drug-related TEAEs were not considered clinically meaningful comparing the OM + AML combination regimens to treatment with OM 20 mg + placebo.

No patients died during Period I or Period II of the study.

During Period I, 6 (0.8%) patients discontinued due to an adverse event. For 3 of the 6 patients on OM 20 mg monotherapy, the adverse event that led to discontinuation was considered by the Investigator to be related to study medication (1 patient with hypotension, 1 patient with increased γ-GT, and 1 patient with irritation and rash on forearms, shanks, hips, abdomen, and back [skin signs of allergia]).

During Period II, 5 (0.9%) patients discontinued due to an adverse event: 2 patients from the OM 20 mg + placebo treatment group, of which 1 (pain in joints) was considered by the Investigator to be related to study medication; 1 patient from the OM 20 mg + AML 5 mg treatment group (dizziness) which was considered to be related to study medication by the

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Investigator; and 2 patients from the OM 20 mg + AML 10 mg treatment group; both of whom were considered by the Investigator to have had an event (peripheral oedema) related to study medication.

In the subgroup analyses, the safety of the OM + AML combination treatment regimens compared to treatment with OM 20 mg + placebo was similar for all age groups, for both males and females, and for both categories of hypertension severity.

There were no laboratory measurements that signified a safety concern. There were no clinically meaningful changes in potassium levels or in renal function in any of the 3 treatment groups. In the OM + AML combination regimens, there were similar increases in platelet counts; a decrease in platelet counts occurred in the OM 20 mg + placebo treatment group. These increases were not considered clinically meaningful. Furthermore, there were no clinically meaningful changes in heart rates, ECGs, or physical examinations when the combinations of OM and AML were compared to treatment with OM 20 mg + placebo.

Conclusions: The combinations of OM 20 mg administered together with AML 5 mg and AML 10 mg both reduced mean sitting DBP to a significantly greater extent compared to therapy with OM 20 mg + placebo. Similar results were observed for mean sitting SBP and 24-hour BP measured by ABPM. The combination of OM 20 mg + AML 10 mg resulted in the greatest mean reductions in sitting DBP, SBP, and the ambulatory derived BP measurements. The greater reductions in BP observed with combination treatment translated into significantly more patients achieving pre-defined BP goal in both OM + AML combination treatment groups compared to the OM 20 mg + placebo treatment group. In the subgroup analyses, the efficacy and safety of the OM + AML combination treatment regimens compared to the OM 20 mg + placebo treatment regimen was similar for all age groups, for both males and females, and for both categories of hypertension severity. Outside of a small increase in the incidence of peripheral oedema in the OM 20 mg + AML 10 mg treatment group compared with the OM 20 mg + placebo treatment group, the addition of AML to OM did not result in any safety findings that were clinically meaningful. The trial confirmed a positive benefit-risk ratio for both OM + AML combination dosages.

Date of the Report: Final – 26 March 2007