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REPORT SYNOPSIS

Name of Sponsor/Company: Daiichi Sankyo Europe GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: CS-866		
Name of Active Ingredient: Olmesartan Medoxomil (OM)		

Title of Study:	Effect of Olmesartan Medoxomil on Arterial Stiffness and Thickness in Subjects with Metabolic Syndrome. DSE-866/47. 2007-003131-23
Phase of Development:	Phase 3b, Pilot study
Study Period:	First subject first visit date: 18 Sep 2008 Last subject last follow-up date: 8 Aug 2011
Coordinating Investigator:	[redacted]
Study Center(s):	The study was conducted in 24 European investigative centres and 10 ECHO centres (for echocardiographic measurements).
Publication (reference):	None
Study Objectives:	<u>Primary objective</u> To investigate in a descriptive way the effect of OM (independent of dosage strength, ie, not distinguishing between 20 mg, 40 mg, and 80 mg) on aortic stiffness by • The change from baseline in carotid femoral Pulse Wave Velocity (PWV) after 52 weeks of double-blind treatment. <u>Secondary objectives</u> To investigate in a descriptive way the effect of OM (independent of dosage strength, ie, not distinguishing between 20 mg, 40 mg, and 80 mg) on the following parameters: • The change from baseline in carotid-femoral PWV after 24 weeks of double-blind treatment. • The change from baseline in carotid-femoral PWV, after adjustment for change from baseline in Mean Blood Pressure (MBP) after 52 and 24 weeks of double-blind treatment. • The change from baseline in Blood Pressure (BP), assessed by conventional blood pressure (BP) measurement and 24h Ambulatory BP Measurement (24h-ABPM) after 52 and 24 weeks of double-blind treatment. • The change from baseline in Pulse Pressure (PP) and Augmentation Index (AI) after 52 and 24 weeks of double-blind treatment. • The change from baseline in common carotid stiffness, Intima-Media Thickness (IMT), and diastolic external diameter after 52 and 24 weeks of double-blind treatment. Furthermore, to investigate in a descriptive way the dose-dependent effect of OM 20 mg, 40 mg, and 80 mg on the following parameters: • The change from baseline in carotid-femoral PWV after 52 and 24 weeks of double-blind treatment. • The change from baseline in carotid-femoral PWV, after adjustment for change from baseline in MBP after 52 and 24 weeks of double-blind treatment. • The change from baseline in BP, assessed by conventional BP

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	measurement and 24h-ABPM after 52 and 24 weeks of double-blind treatment. • The change from baseline in PP and AI after 52 and 24 weeks of double-blind treatment. • The change from baseline in common carotid stiffness, IMT, and diastolic external diameter after 52 and 24 weeks of double-blind treatment.
Study Design:	This was a Phase 3b, multi-centre, double-blind, randomized, parallel-group study, in which subjects were assigned into three treatment groups and received either OM 20 mg, OM 40 mg, or OM 80 mg, once a day (o.d.). Each group received OM 20 mg at baseline. After one month, two-third of subjects switched to OM 40 mg. After another month, one-third of subjects switched to OM 80 mg. The forced titration for the 40 mg and 80 mg dose was to avoid side effects by treating subjects with a high dose from first instance.
Study Duration	The study was divided in 2 main periods: A 3-week placebo run-in period: during this period that started after the Screening visit, subjects were administered a placebo (OM matching placebo tablets). A 52-week Double-Blind Treatment period as follows: dose group 1 with OM 20 mg for the entire 52 weeks, dose group 2 with OM 20 mg for 4 weeks, followed by OM 40 mg for 48 weeks, and dose group 3 with OM 20 mg for 4 weeks, followed by OM 40 mg for another 4 weeks, and OM 80 mg for 44 weeks. Subjects were asked at the judgment of the Investigator to return to the clinical centre to perform an SFU visit in case of ongoing AEs between 1 and 2 weeks after the End of Treatment (i.e., after final examination [FE] visit or after premature termination [PT] visit). The maximum study duration was 57 weeks per subject.
Number of Subjects:	Recruited: 264 In the original protocol it was planned to recruit 350 subjects and to randomize 318 subjects with hypertension and metabolic syndrome. The study experienced a significantly reduced recruitment rate. The original protocol was amended, and in the amendment, the stop date for the recruitment was fixed which resulted into 264 recruited subjects. Screened: 258 Enrolled/Randomized: 258/133 Completed/Discontinued: 111 / 22
Diagnosis and Main Criteria for Study Entry:	**Key inclusion criteria** Subjects had to satisfy all of the following criteria at Screening visit (Visit 1) and at Baseline (Visit 2) to be included in the study; except inclusion criterion 3, which needed only to be satisfied at the Screening visit: 1) Male and female outpatients 2) Age ≥ 18 and ≤ 75 years

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3) Hypertension and metabolic syndrome defined, according to the ATP III/ IDF 2005 and ESH/ESC 2007 definitions with modifications, as:
   a) BP ≥ 130/85 mmHg and < 150/95 mmHg (ie, untreated high normal BP or "low range" mild hypertension) and at least 1 of the following traits:
      - Abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women)
      - Triglyceride level ≥ 150 mg/dL
      - High Density Lipoprotein (HDL)< 40 mg/dL for men and < 50 mg/dL for women
      - Fasting blood glucose ≥ 110 mg/dL and < 126 mg/dL (ie, no type 2 diabetes)

      Or
   b) BP ≥ 120/80 mmHg and < 130/85 mmHg (ie, normal BP) and one antihypertensive treatment at Screening, and normal to "low range" mild hypertension (ie, ≥ 130/85 and < 150/95 mmHg) at Baseline, and at least 1 of the following traits:
      - Abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women)
      - Triglyceride level ≥ 150 mg/dL
      - HDL < 40 mg/dL for men and < 50 mg/dL for women
      - Fasting blood glucose ≥ 110 mg/dL and < 126 mg/dL (ie, no type 2 diabetes)

      Or
   c) BP ≥ 130/85 mmHg and < 150/95 mmHg (ie, untreated high normal BP or "low range" mild hypertension) and current treatment with a lipid-lowering agent and at least 1 of the following traits:
      - Abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women)
      - Fasting blood glucose ≥ 110 mg/dL and < 126 mg/dL (ie, no type 2 diabetes)
4) No anti-hypertensive treatment or treatment with only one anti-hypertensive medication within the last 3 months (including ACE, ARB and renin-inhibitors).

Exclusion criteria

Subjects who met any one of the following criteria at Screening visit (Visit 1) or at Baseline (Visit 2) were disqualified from entering the study:

1) Pregnant or lactating female (prerequisite for female subjects of childbearing potential: adequate contraception)

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2) Type 1 and type 2 diabetes
3) "High range" mild hypertension (ie, Systolic Blood Pressure [SBP]: 150 - < 160 mmHg and/or Diastolic Blood Pressure [DBP]: 95 - < 100 mmHg)
4) Moderate, severe, or resistant hypertension (see definitions below)

	SBP (mmHg)		DBP (mmHg)
Moderate hypertension	160 – 179	and/or	100 – 109
Severe hypertension	≥ 180	and/or	≥ 110
Resistant hypertension	Hypertension resistant to treatment		

5) Secondary hypertension of any aetiology, such as renal disease, pheocromocytoma, or Cushing's syndrome
6) Serious disorders which could limit the ability to evaluate the efficacy or safety of the study drug, including cerebrovascular, cardiovascular, renal, respiratory, hepatic, gastrointestinal, endocrine, metabolic, hematological, oncological, neurological, or psychiatric diseases
7) History of the following pathologies within the last 6 months: myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, heart failure, hypertensive encephalopathy, stroke, or transient ischemic attack
8) Clinically relevant abnormal laboratory values
9) Contraindication to OM
10) Previously screened subjects, unless they failed inclusion criterion 3 at screening and/or baseline under earlier protocol requirements.
11) Alcohol or drug of abuse in the past 2 years
12) Planned hospitalization during the study period
13) Participation in any other clinical study within 30 days prior to Screening
14) Enrollment of the Investigator(s), site staff, or their family members

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Investigational Product and Comparator Information:

Dosage Form: three doses of OM (20 mg, 40 mg, or 80 mg) were administered

Route of Administration: orally

Lot No: [redacted] (OM 20 mg), [redacted] (matched placebo OM 20 mg), [redacted] (OM 40 mg), [redacted] (matched placebo OM 40 mg)

Packaging Information:

The box for the 3-week Placebo Run-in period (Visit 1 to Visit 2) contained 2 blisters with twenty 20-mg OM matching placebo tablets each. Subjects were to take one tablet once daily (o.d.) immediately before breakfast for three weeks.

Treatment period: the box for the first 4 weeks of treatment, titration period month 1 (Visit 2 to Visit 3) contained five blisters. Each blister contained seven 20-mg OM tablets and fourteen 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 20-mg OM and two placebo) o.d. immediately before breakfast for one month.

For the 4 weeks after the first up-titration, titration period month 2 (Visit 3 to Visit 4), there were three kinds of boxes:

- 20-mg OM group: five blisters; each blister contained seven 20-mg OM tablets and fourteen 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 20-mg OM and two placebos) o.d. immediately before breakfast for one month.
- 40-mg OM group: five blisters; each blister contained seven 20-mg OM matching placebo tablets; seven 40-mg OM tablets, and seven 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 40-mg OM and two placebos) o.d. immediately before breakfast for one month.
- Box for potential down-titration to placebo treatment (for subjects of the 20-mg OM group): five blisters; each blister contained seven 20-mg OM matching placebo tablets and fourteen 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 20-mg OM matching placebo and two 40-mg OM matching placebo) o.d. immediately before breakfast for the remaining study period.

For the 4 weeks after the second up-titration (Visit 4 to Visit 5), there were four kinds of boxes:

- 20-mg OM group: five blisters; each blister contained seven 20-mg OM tablets and fourteen 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 20-mg OM and two placebo) o.d. immediately before breakfast the remaining study period.
- 40-mg OM group: five blisters; each blister contained seven 20-mg OM matching placebo tablets; seven 40-mg

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OM tablets, and seven 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 40-mg OM and two placebo) o.d. immediately before breakfast the remaining study period.

- 80-mg OM group: five blisters; each blister contained seven 20-mg OM matching placebo tablets and fourteen 40-mg OM tablets. Subjects were to take three tablets (two 40-mg OM and one placebo) o.d. immediately before breakfast the remaining study period.
- Box for potential down-titration to placebo treatment (for subjects of the 20-mg OM group): five blisters; each blister contained seven 20-mg OM matching placebo tablets and fourteen 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 20-mg OM matching placebo and two 40-mg OM matching placebo) o.d. immediately before breakfast for the remaining study period.

For the rest of the treatment period (Visits 5 – 7), there were four kinds of boxes:

- 20-mg OM group: five and/or fifteen blisters (depending on duration between two visits); each blister contained seven 20-mg OM tablets and fourteen 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 20-mg OM and two placebo) o.d. immediately before breakfast the remaining study period.
- 40-mg OM group: five and/or fifteen blisters (depending on duration between two visits); each blister contained seven 20-mg OM matching placebo tablets; seven 40-mg OM tablets, and seven 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 40-mg OM and two placebo) o.d. immediately before breakfast the remaining study period.
- 80-mg OM group: five and/or fifteen blisters (depending on duration between two visits); each blister contained seven 20-mg OM matching placebo tablets and fourteen 40-mg OM tablets. Subjects were to take three tablets (two 40-mg OM and one placebo) o.d. immediately before breakfast the remaining study period.
- Box for potential down-titration to placebo treatment (for subjects of the 20-mg OM group): five and/or fifteen blisters (depending on duration between two visits); each blister contained seven 20-mg OM matching placebo tablets and fourteen 40-mg OM matching placebo tablets. Subjects were to take three tablets (one 20-mg OM matching placebo and two 40-mg OM matching placebo) o.d. immediately before breakfast for the remaining study period.

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Note: Down-titration of the study medication was based on judgement of the investigator and could occur at any point in time.		

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Criteria for Evaluation:

Efficacy:

Primary efficacy variable

Change from baseline in carotid-femoral PWV at Week 52 (all three treatment groups combined).

Additional efficacy variables

- Change from Baseline in carotid-femoral PWV at Week 52 (separately for each treatment group)
- Change from baseline in carotid-femoral PWV at Week 24 (all three treatment groups combined as well as separately by treatment group)
- Change from baseline in carotid and aortic PP at Week 24 and Week 52
- Change from baseline in AI at Week 24 and Week 52
- Change from baseline in common carotid IMT at Week 24 and Week 52
- Change from baseline in diastolic external diameter at Week 24 and Week 52
- Change from baseline in carotid stiffness at Week 24 and Week 52
- Change from baseline in carotid compliance at Week 24 and Week 52
- Change from baseline in carotid distensibility at Week 24 and Week 52
- Change from baseline in mean circumferential wall stress (MCWS) at Week 24 and Week 52
- Change from baseline in wall cross-sectional area (WCSA) at Week 24 and Week 52
- Change from baseline in trough sitting BP assessed by the conventional measurements at Week 24 and Week 52
- Change from baseline in 24h-BP assessed by the 24h-ABPM at Week 24 and Week 52

Safety

Primary safety parameters

Adverse Event (AE) profile of OM 20 mg, 40 mg, and 80 mg treatment groups.

Additional safety parameters

Vital signs at screening, baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 52.
12-lead Electrocardiogram (ECG) at screening and Week 52.
Physical examination at Screening, Baseline, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 52.
Clinical hematology, biochemistry and urinalysis at Screening, Baseline, Week 8, Week 24 and at Week 52.

Biomarkers

The following biomarkers were assessed at Visit 2 (Week 4) and 8 (Week 52) or at the PT Visit:
high sensitive C reactive protein (hs-CRP)
high sensitive tumor necrosis factor-alpha (hs-TNF-alpha)
high sensitive interleukine-6 (hs-IL-6).

Statistical Methods:

Statistical Considerations:

Originally, it was planned to recruit 350 subjects and to randomize 318 subjects with hypertension and metabolic syndrome in order to achieve 276 evaluable subjects. Due to difficulties with the recruitment, the sample size was reduced to 264 subjects and as a consequence no confirmatory analysis could be performed. The original protocol was amended and all results were interpreted in a purely

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descriptive/explorative way. In reality, the study recruitment did not reach 350 or 264 subjects. Actually, 258 subjects entered the Placebo Run-in period to randomize 133 subjects with hypertension and metabolic syndrome.

Statistical Analysis for the Primary Endpoint:

The analysis was descriptive and focused on the changes of PWV after 52 weeks: Change in PWV was analyzed by first performing a paired t-test on the change from baseline for all three treatment groups combined. In case normality does not hold (checked graphically), a Wilcoxon signed-rank test was performed too.

Statistical Analysis for the Secondary Endpoints:

The analysis was descriptive and focused on changes from baseline for the additional efficacy variables. Changes from baseline were analyzed by first performing a paired t-test on the change from baseline for all three treatment groups combined as well as the single treatment groups. Treatment differences were assessed via an ANCOVA model with treatment as factor and baseline value as covariate, in case a significant change (either for the combined groups or for at least one of the single treatment groups) was found. Both, the OM 40 mg and OM 80 mg dose groups were compared to the OM 20 mg group. Corresponding confidence intervals for the differences between the groups were provided.

For the changes from baseline in PWV, at Week 52 last observation carried forward (LOCF), a second ANCOVA model was performed with treatment as a factor and the baseline PWV and the change from baseline in carotid MBP as covariate. Again, the interpretation of all p-values was purely descriptive/explorative.

The above described analyses were based on the full analysis set (FAS) using the LOCF and observed case (OC) approach. As the difference between the FAS and the per protocol set (PPS) was less than 20%, no additional analysis based on the PPS was performed.

Results

Efficacy Results

Primary Efficacy Endpoint

For the primary efficacy endpoint, ie, change from baseline in PWV at Week 52 for the combined treatment group, a statistically significant ($p < 0.0001$) difference in change from baseline was observed.

Secondary Efficacy Endpoints

Results for the secondary efficacy endpoints referring to ECHO measurements are summarized below:

Pulse Wave Velocity

The change from baseline in PWV at Week 52 was not statistically significant for the OM 20 treatment group and was statistically significant for the 40 mg and 80 mg treatment groups and at Week 24 was statistically significant for the OM 20, 40, and 80 mg treatment groups. No between group differences were observed when OM 40 mg and OM 80 mg treatment groups were compared to the OM 20 mg group, in an ANCOVA model with baseline value as covariate and treatment as factor, nor as in an ANCOVA model with baseline value and carotid MBP as covariates and treatment as a factor).

Carotid PP and Aortic PP

The changes from baseline in carotid PP and aortic PP at Week 52 and Week 24 were statistically significant for the OM 20, 40, and 80 mg treatment groups.

Augmentation index

The change from baseline for AI at Week 52 was not statistically significant for the OM 20 mg treatment group and was statistically significant for the OM 40 and 80 mg treatment groups. At Week 24, changes from baseline in AI were statistically significant for the OM 20 and 40 mg treatment groups but not for the 80 mg treatment groups.

Common carotid IMT

The changes from baseline in common carotid IMT at Week 52 and Week 24 were not statistically

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significant for the OM 20, 40, and 80 mg treatment groups.

Diastolic external diameter

The change from baseline in diastolic external diameter at Week 52 was not statistically significant for the OM 20 and 40 mg treatment groups but was statistically significant for the 80 mg treatment group. At Week 24, the changes from baseline were statistically significant for the OM 40 and 80 mg treatment groups but not for the 20 mg treatment group.

Carotid stiffness

The change from baseline in carotid stiffness at Week 52 was not statistically significant for the OM 20 mg treatment group, but was statistically significant for the OM 40 and 80 mg treatment groups. At Week 24, the change from baseline was statistically significant for the OM 40 mg treatment group but not for the 20 and 80 mg treatment groups.

Carotid distensibility

The change from baseline in carotid distensibility at Week 52 and Week 24 was not statistically significant for the OM 20 mg treatment group, but was statistically significant for the OM 40 and 80 mg treatment groups.

Carotid compliance

The change from baseline in carotid compliance at Week 52 and Week 24 was not statistically significant for the 20 and 80 mg OM treatment groups, but was statistically significant for the OM 40 mg treatment group.

MCWS

The changes from baseline in MCWS at Week 52 and Week 24 were statistically significant for the OM 20, 40, and 80 mg treatment groups.

WCSA

The changes from baseline in WCSA at Week 52 and Week 24 were not statistically significant for the OM 20, 40, and 80 mg treatment groups.

For all the secondary efficacy variables referring to ECHO measurements, no between group differences were observed when OM 40 mg and OM 80 mg treatment groups were compared to the OM 20 mg group, except for the difference in change from baseline at Week 24 for MCWS between the 40 mg and the 20 mg treatment group.

For the secondary efficacy endpoints referring to the conventional trough blood pressure measurements, the changes from baseline at Week 52 and Week 24 were statistically significant for the OM 20, 40, and 80 mg treatment groups. No between group differences were observed when OM 40 mg and OM 80 mg treatment groups were compared to the OM 20 mg group, except for sitting SBP and sitting DBP for the OM 80 mg compared to the OM 20 mg treatment group at Week 24 and for sitting DBP the OM 40 mg compared to the OM 20 mg treatment group at Week 52.

For the secondary efficacy endpoints referring to the ABPM measurements, the changes from baseline at Week 52 and Week 24 were statistically significant for the OM 20, 40, and 80 mg treatment groups. No between group differences were observed between OM 40 and 80 mg compared to the OM 20 mg treatment group.

The changes from baseline in binary dipper status using a chi-square test was statistically significant for the OM 80 mg treatment group at Week 24 and for the 40 mg treatment group at Week 52.

Exploratory Efficacy Analyses

Using the LOCF approach at Week 52, the plots show that the regression lines for the different treatment groups are crossing and no downward shift of the PWV-MBP curve could be observed to indicate that PWV is reduced to a greater extent with the highest dose (80 mg). This is in line with no significance difference between the treatment groups when including the MBP into the ANCOVA model.

Sensitivity analysis
A sensitivity analysis was performed by repeating the analysis of the within-group changes (all treatment groups combined as well as single treatment groups) and – if applicable – of the ANCOVA analysis for the primary and all secondary variables by excluding centre 1103 (after site audit by the sponsor). In general no major differences were observed compared to the original efficacy analysis after excluding the centre 1103.

Safety Results
Two subjects in this study died; 1 subject during double-blind treatment (sudden death) and 1 subject during the placebo run-in period (cardiac arrest and coma). Serious adverse events (SAEs) were reported for 9 subjects during double-blind, including the subject who died. During placebo run-in, no SAEs had occurred apart from the fatal event. None of the SAEs (including the fatal events) were considered drug-related by investigator and/or sponsor.
At least one Treatment-emergent AE (TEAE) was experienced by 91 of the 133 subjects (68.4%) for the overall double-blind treatment period. The overall incidence of subjects with a TEAE was higher in the OM 40 mg and 80 mg treatment groups (76.2% and 72.3%, respectively) compared to the OM 20 mg treatment group (56.8%). Most TEAEs were mild to moderate in severity. The number of subjects with at least one severe TEAE was 8 (6.0%) overall, i.e., 2 (4.5%), 3 (7.1%) and 3 (6.4%) subjects in the OM 20, 40 and 80 mg treatment groups, respectively.
Treatment-emergent drug-related AEs leading to early treatment discontinuation were reported for 4 subjects (3.0%). For 2 of these subjects (both in the OM 40 mg treatment group) the reason for discontinuation was sustained hypotension. For 3 other subjects who discontinued treatment early due to an AE, the AE leading to discontinuation was not considered related to the study medication by investigator and/or sponsor.
Regardless of treatment group or period, the most frequent TEAEs in the overall double-blind treatment period (≥ 5% overall) were hypotension in 10 subjects (7.5%), nasopharyngitis in 8 subjects (6.0%), and bronchitis, back pain, and influenza each in 7 subjects (5.3%). Hypotension was reported in 2 (4.5%), 5 (11.9%) and 3 (6.4%) subjects in the OM 20, 40 and 80 mg treatment groups, respectively.
Hypotension was the only drug-related TEAE that occurred in ≥ 5% in at least one dose group.
There were no clinically meaningful differences between the three treatment groups for laboratory parameters, physical findings, or ECG parameters.

Biomarkers
No significant changes in hs-CRP, hs-TNF-alpha and hs-IL-6 concentrations were observed.

Conclusions:

Efficacy

Olmesartan had an impact on the main important parameter predicting arterial stiffness. Overall the study concluded that olmesartan was able to remodel the arterial wall enough (chronic inward remodeling) in order to reduce the stiffness of the arterial wall material and thus reduce arterial stiffness

Safety
OM was safe and well tolerated in subjects with hypertension administered doses of 20, 40, or 80 mg in this study.

Date of the Report: 30 July 2012 (Version 2.0)