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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		

Title of Study:	Effects of angiotensin-receptor blockade with olmesartan on carotid atherosclerosis in patients with hypertension: the CONFIRMatory olmesartan plaque regression study (CONFIRM). Protocol number: DSE-OLM-01-09. EudraCT number: 2009-013342-92
Phase of Development:	4
Study Period:	First subject first visit date: 09 Jun 2010 Last subject completed date (excluding safety follow-up): 04 Jul 2011
Investigator(s):	Coordinating investigator: [redacted] For a full list of the investigators participating in the study, see Appendix 16.1.4.
Study Center(s):	There were 2 different types of study site: Recruitment Sites and Ultrasonographic (US) Sites. A total of 15 US and 80 Recruitment sites (10 to 12 sites per country) were planned. In practice, there was a total of 72 Recruitment Sites, 3 US Sites and 11 sites that were both US and Recruitment Sites. Sites were located in the following countries: Belgium, Czech Republic, Germany, Italy, Poland, Romania, and The Netherlands.
Publication (reference):	None.
Study Objectives/Hypothesis:	The primary objective of this study was to compare, in a descriptive/exploratory way, the effect of olmesartan medoxomil (OM) and atenolol (ATE) on absolute changes of carotid plaque volume (PV) as assessed by 3-D ultrasonography at the last available evaluation after baseline (after at least 26 weeks of treatment) compared to baseline. The secondary objectives were to: • Compare the effect of OM and ATE on percentage change of PV from baseline to last available evaluation after baseline. • Compare the effect of OM and ATE on absolute changes in seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) from baseline to last available evaluation after baseline. • Compare the effect of OM and ATE on absolute changes of PV from baseline to last available evaluation after baseline after adjustments for changes in SeDBP and SeSBP from baseline. • Assess safety and tolerability of OM and ATE during the study. Exploratory objectives were to: • Determine the effect of OM and ATE on absolute changes in intima media thickness (IMT) of the common carotid (CC) artery from baseline to last available evaluation after baseline. • Determine the effect of OM and ATE on absolute changes in lumen diameter (LD) of the CC artery from baseline to last available evaluation after baseline. • Determine the changes in (categorised) PV from baseline (2 categories based on split at median of the combined treatment

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	groups at baseline) from baseline to last available evaluation after baseline. • Determine the effect of OM and ATE on absolute changes in plaque surface, plaque texture and plaque echogenicity from baseline to last available evaluation after baseline. • Assess the proportion of subjects with decreased, increased or unchanged PV from baseline to last available evaluation after baseline. • Determine the effect of OM and ATE on high sensitivity C-reactive protein (hsCRP) from baseline to last available evaluation after baseline.
Study Design/Methodology:	This was a phase 4 randomised, double-blind, double-dummy, parallel-group, multi-national, multi-centre study. The study design consisted of a taper-off screening period followed by a titration period of up to 6 phases of 4 weeks, a maintenance period (54 weeks) and a taper-down period (approximately 1 week). Screening Period: To assess subject eligibility by ultrasonography, demographic data, electrocardiogram (ECG), physical examination, blood pressure (BP), laboratory values, and check of inclusion/exclusion criteria. A taper-off period for subjects on antihypertensive treatment (at the discretion of their treating physician, all others were to start with double-blind treatment). Treatment Phase A (Week 0): Subjects who met the inclusion criteria were randomised to either 20 mg OM once daily (o.d.) or 50 mg ATE o.d. Treatment Phase B (Week 4): Subjects not reaching BP goals (SeSBP/SeDBP < 140/90 mmHg or for subjects with cerebrovascular disease or renal dysfunction SeSBP/SeDBP < 130/80 mmHg) received the doubled dose of study medication (40 mg OM o.d. or 100 mg ATE o.d., respectively). Treatment Phase C (Week 8): Subjects not reaching BP goals received additional treatment with open-label 12.5 mg hydrochlorothiazide (HCTZ). Treatment Phase D (Week 12): Subjects not reaching BP goals received, in addition, the increased dose HCTZ 25 mg. Treatment Phase E (Week 16): Subjects not reaching BP goals received, in addition, treatment with open-label 1 mg or 2 mg doxazosin at the discretion of the investigator. The other medication given so far was kept. Treatment Phase F (Week 20): Subjects not reaching BP goals received an increased dose of doxazosin up to 4 mg in addition. The other medication given so far was kept. Treatment Phase G (Week 24 to Week 78, end of study): Subjects were kept on the treatment of either treatment Phase A, B,

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	C, D, E or F. At the discretion of the investigator, down- or up-titration was possible at any time (open-label HCTZ and doxazosin). After Treatment Phase G, subjects were to enter the taper-down period. From the end of treatment Phase F (Week 24) until the end of the study, subjects whose SeSBP was ≥ 150 mmHg and/or SeDBP ≥ 100 mmHg during 2 consecutive visits after receiving the full dose of all medications were to be withdrawn from the study.
Duration of Treatment for Individual Subject:	The individual treatment duration was planned to be 18 months in total (78 weeks).
Number of Subjects:	Planned: 408 (204 subjects in each treatment arm) Screened/Enrolled: 964 Randomised: 114 (56 to OM and 58 to ATE) Completed according to the study protocol: 0/114 Discontinued before early study termination: 29/114 Discontinued after early study termination: 85/114
Diagnosis and Main Criteria for Study Entry:	Major inclusion criteria were: 1. Male and female Caucasian outpatients aged > 40 years. 2. High BP defined as mean SeSBP/SeDBP ≥ 140/90 mmHg. 3. One or more of the following additional risk factors: • Smoking; • Dyslipidaemia (high-density lipoprotein cholesterol < 0.9 mmol/L or low-density lipoprotein cholesterol > 2.6 mmol/L, or triglycerides > 1.7 mmol/L); • Left ventricular hypertrophy; • Cardiocerebrovascular events > 6 months ago; • Presence of target organ damage. 4. Non-calcified (not marked shadowing) plaque in the CC artery, in the internal carotid artery or the carotid bulb with a PV ≥ 0.040 cm^3 (≥ 40 µL) according to the measurements of the European Ultrasound Teaching and Reading Centre. Major Exclusion Criteria were: 1. Secondary or high grade hypertension including grade III hypertension (SeSBP of > 180 mmHg or SeDBP of > 105 mmHg). 2. Stroke, myocardial infarction within the previous 6 months. 3. Interventional or surgical vascular treatment within the previous 3 months. 4. Presence of significant narrowing of the aortic or bicuspid valve and severe obstruction of cardiac outflow (hypertrophic cardiomyopathy).

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	5. Symptomatic heart failure. 6. Diabetes. 7. Chronic obstructive pulmonary disease or asthma. 8. Claudicatio intermittens stage II b or higher. 9. Clinical evidence of severe renal disease (including renovascular occlusive disease, nephrectomy and/or renal transplant, creatinine clearance of < 30 mL/min, macroalbuminuria [> 300 mg albumin/24 hours or 300 µg albumin/mg creatinine]). 10. Treatment with angiotensin converting enzyme-inhibitors or angiotensin-receptor blockers during last 3 months. 11. Start of treatment with a lipid-lowering agent or modification of dosage within last 3 months. 12. Electrocardiographic evidence of second or third degree atrioventricular block, atrial fibrillation, cardiac arrhythmia (requiring therapy) or bradycardia (< 50 bpm at rest). 13. Known intolerance to study drugs. 14. Impaired liver function tests suggesting severe liver disorder. 15. Any life threatening disease. 16. Duplexsonographically determined stenosis of the common or internal carotid artery > 75%. 17. Plaque with marked shadowing from calcification. 18. Target plaques in CC artery extending into both internal and external arteries.
Investigational Product, Comparator and Other Formulations Information:	Investigational Product: Dosage Form and Dose: OM 20 mg (low dose) and 40 mg (high dose) tablets and matching placebo. Route of Administration: Oral Lot No.: OM 20 mg: [redacted] Matching placebo OM 20 mg: [redacted] OM 40 mg: [redacted] Matching placebo OM 40 mg: [redacted] Packaging Information: Double aluminium blisters. Packaging was performed by Daiichi Sankyo Europe GmbH. Comparator: Dosage Form and Dose: ATE 50 mg (low dose) and 100 mg (high dose) tablets and matching placebo Route of Administration: Oral Lot No.: ATE 50 mg: [redacted] Matching placebo ATE 50 mg: [redacted] ATE 100mg: [redacted]

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Matching placebo ATE 100 mg: [redacted]
Packaging Information: As OM.
Other formulations:
Dosage Form: HCTZ 12.5 mg and 25 mg tablets
Route of Administration: Oral
Lot No.: HCTZ 12.5 mg: [redacted]
HCTZ 25mg: [redacted]
Packaging Information: Original commercial polyvinylchloride/polyvinylidene chloride blisters secondarily packaged in wallet cards.
Dosage Form: Doxazosin mesylate (doxazosin) 2 mg and 4 mg tablets
Route of Administration: Oral
Lot No.: Doxazosin 2 mg: [redacted]
Doxazosin 4 mg: [redacted]
Packaging Information: As HCTZ.

Criteria for Evaluation:

The primary efficacy variable for this study was the absolute change from baseline (Week 0) in mean PV (cm^3) as assessed by 3-D ultrasonography to the last available evaluation after baseline (and at least 26 weeks after randomisation).

The secondary efficacy variables were:

- Percentage change from baseline in mean PV to last available evaluation after baseline.
- Absolute change from baseline in mean SeDBP and mean SeSBP to last available evaluation after baseline.
- Percentage change from baseline in mean PV to last available evaluation after baseline after adjustment for change in mean SeDBP and mean SeSBP.

Exploratory efficacy variables

Quantitative exploratory variables:

- Absolute change from baseline to last available evaluation after baseline in mean IMT of the CC artery of the leading side (IMT_{lead}) (cm) (based on 3 measurements).
- Absolute change from baseline to last available evaluation after baseline in mean IMT of the CC artery of the less affected side (IMT_{less}) (cm) (based on 3 measurements).
- Absolute change from baseline to last available evaluation after baseline in overall mean IMT (IMT_{mean}) (cm) ie mean of both carotid arteries.
- Absolute change from baseline to last available evaluation after baseline in LD of the CC artery measured at end-diastole on the leading side of the neck (LD_{lead}) (cm)
- Absolute change from baseline to last available evaluation after baseline in LD of the CC artery measured at end-diastole on the less-affected side of the neck (LD_{less}) (cm)
- Absolute change from baseline to last available evaluation after baseline in mean cross-sectional area of IMT (CSA-IMT) calculated for the mean IMT on the leading side as well as for the mean IMT on the less affected side (ie IMT_{lead}, IMT_{less}) where mean CSA-IMT (cm^2) was specified by the formula:

  $CSA\text{-}IMT_i = \pi \times IMT_i \times (IMT_i + LD_i)$ with i = lead, less
- Percentage change from baseline to last available evaluation after baseline in plaque echogenicity

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(assessed as quantitative variable) (%). The quantitative assessment of the plaque echogenicity was done by grey-scale analysis based on tissue harmonic imaging (THI).

- Absolute change from baseline hsCRP (mg/L) to the last available evaluation after baseline.

Qualitative/categorical exploratory variables:

- Frequencies of subjects with a PV with:

  $PV \leq MED_{PV\_baseline}$ or $PV > MED_{PV\_baseline}$

  at last available evaluation after baseline, respectively, where $MED_{PV\_baseline}$ was the median of mean PV at baseline of all subjects, ie, disregarding treatment groups.
- Frequencies of subjects with a *smooth, irregular or ulcerated* plaque surface at last available evaluation after baseline. The qualitative assessment of the 3 categories (*smooth, irregular, ulcerated*) was based on THI.
- Frequencies of subjects with a *hyperechogenic, shadowing, lipid core, isoechogenic or anechogenic* plaque echogenicity (assessed as categorised variable) at last available evaluation after baseline. The qualitative assessment of the 5 categories (*hyperechogenic, shadowing, lipid core, isoechogenic, anechogenic*) was based on THI.
- Frequencies of subjects with a *homogenous or heterogenous* plaque texture at last available evaluation after baseline. The qualitative assessment of the 2 categories (*homogenous, heterogenous*) was based on THI.
- Frequencies of subjects with *decreased, increased or unchanged* mean PV at last available evaluation after baseline.

Safety

Safety assessments included adverse events (AEs), clinical laboratory parameters (biochemistry, haematology, urinalysis, and pregnancy), 12-lead ECG, physical examination, and vital signs.

Statistical Methods:

Due to the early termination of the study and the low number of data available, no efficacy analysis was carried out, but efficacy endpoints for all efficacy variables (primary, secondary and exploratory) were listed.

Summary:

Note: the study was terminated early on 16 May 2011 due to difficulties in recruiting eligible subjects. Enrolment was stopped on 16 May 2011 and subjects already enrolled in the study were required to be withdrawn from the study. The primary efficacy parameter as well as all secondary efficacy and exploratory variables that referred to the PV or attributes of the plaque should have been analyzed only on subjects that had been treated for at least 26 months. Due to the early termination of the study, the analysis set (the Full Analysis Set I) comprised only 29 subjects. Therefore, it was decided not to perform the efficacy analysis and to only provide the listings.

Efficacy Results: Not applicable; only listings are provided in Appendix 16.2.

Safety Results:

- Overall, study medications were safe and well tolerated by the subject population in this study.
- The safety profile and incidence of TEAEs were comparable in the OM and ATE treatment groups, with 42.6% and 41.1% of the subjects reporting at least 1 TEAE with OM and ATE, respectively, during the double-blind treatment period. Most TEAEs were mild or moderate in severity and mostly related to infections and infestations, nervous system disorders, gastrointestinal disorders, and general disorders and administration site conditions. The most common TEAEs with OM were asthenia and headache, which were each reported by 3 subjects.

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The most common TEAE with ATE was upper respiratory tract infection, which occurred in 4 subjects.

- OM and ATE were also comparable regarding the incidence of TEAEs that were considered to be related to the study medication, with 8 subjects at each treatment group experiencing at least 1 drug-related TEAE. Drug-related TEAEs were mostly related to nervous system disorders and general disorders and administration site conditions. The most common drug-related TEAE was headache, which was reported by 3 subjects with OM. Drug-related vertigo and asthenia were experienced by 2 subjects each with OM. For subjects taking ATE, drug-related bradycardia and increased BP were each reported by 2 subjects. All other drug-related TEAEs were reported by 1 subject at each treatment group. Most drug-related TEAEs were mild or moderate in severity and recovered at the end of the study.
- Six subjects treated with OM and 4 subjects treated with ATE experienced at least 1 drug-related TEAE that was considered to be significant (defined as non-serious laboratory TEAE or a non-serious TEAE with any corrective action taken with study medication or any other action taken). The most common drug-related significant TEAEs were vertigo, asthenia, headache, chest pain, dizziness, mood altered and hypotension with OM; and bradycardia, asthenia, malaise, increased BP, dizziness, headache, depressive symptom and insomnia with ATE. Drug-related TEAEs of special interest were reported by 6 subjects with OM (headache, vertigo, asthenia, BP decreased, dizziness and hypotension) and 2 subjects with ATE (asthenia, dizziness and headache).
- Only 1 subject experienced a serious TEAE during the double-blind treatment phase. This was an event of unstable angina which was considered to be not related to study treatment with ATE and resolved 15 days after the onset of the SAE. Also, non-treatment emergent SAEs occurred in 2 subjects who reported an SAE during the taper-off phase before starting study treatment (chest pain, and back pain and osteoarthritis), and in 2 subjects who did not stay more than 1 day in the study and reported an SAE of unstable angina before randomisation. All of these events resolved. No drug-related SAEs were reported in the study. No subjects died during the study.
- Six subjects treated with OM and 5 subjects treated with ATE reported at least 1 TEAE leading to discontinuation from the study, most of which were considered to be related to the study treatment. Drug-related TEAEs leading to study discontinuation were vertigo, asthenia, headache, chest pain, mood altered and hypotension with OM; and bradycardia, asthenia, malaise, Increased BP, dizziness, headache, depressive symptom and insomnia with ATE.
- Laboratory data, vital signs, physical examination and ECG data did not reveal any safety concerns.

Pharmacokinetic/Pharmacodynamic Results: Not applicable.

Other Results: Not applicable.

Conclusions:

After a mean exposure to double-blind treatment of approximately 20 weeks before the early termination of the study, both OM and ATE, administered in individually optimised dosages of 20 to 40 mg OM and 50 to 100 mg ATE, were safe and generally well tolerated in the hypertensive subject population studied. The safety findings and the incidence of TEAEs of both OM and ATE were consistent with the known safety profile of the study drugs. No safety concerns were identified during the course of the study.

Date of the Report: 10 Jan 2012