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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-8635		
Name of Active Ingredient: olmesartan medoxomil + amlodipine besylate + hydrochlorothiazide		

Title of Study:	A Randomised, Double-Blind, Add-On Study of Hydrochlorothiazide in Subjects With Moderate to Severe Hypertension Not Achieving Target Blood Pressure on Olmesartan Medoxomil/Amlodipine Fixed Dose Combination 40/10 mg Alone
Phase of Development:	3
Study Period:	First subject first visit date: 29 April 2009 Last subject last follow-up date: 07 September 2010
Investigators:	See Appendix 16.1.4 for a complete list of investigators
Study Centers:	187 investigative centres in Europe
Publication (reference):	None
Study Objectives:	The main purpose of this study was to determine if additional antihypertensive efficacy is gained by the addition of hydrochlorothiazide (HCTZ) to the fixed-dose combination of olmesartan medoxomil (OM) 40 mg and amlodipine (AML) 10 mg in subjects with moderate to severe hypertension not adequately controlled on OM/AML alone. **Period II (Week 8 to Week 16) – Primary Objective:** The primary objective of this study was to demonstrate that additional antihypertensive efficacy for seated diastolic blood pressure (SeDBP) is gained by adding HCTZ 12.5 mg or HCTZ 25 mg to the treatment regimen in subjects with moderate to severe hypertension not adequately controlled on OM/AML 40/10 mg alone at Week 16 (after 8 weeks of double-blind treatment) using conventional blood pressure measurement. **Period II (Week 8 to Week 16) – Secondary Objectives:** The secondary objectives for Period II included the following: • To evaluate the antihypertensive efficacy for SeDBP of the triple combinations of OM/AML/HCTZ 40/10/12.5 mg and OM/AML/HCTZ 40/10/25 mg compared to OM/AML 40/10 mg at Week 12 (after 4 weeks of double-blind treatment) using conventional blood pressure measurement. • To evaluate the antihypertensive efficacy for seated systolic blood pressure (SeSBP) of the triple combinations of OM/AML/HCTZ 40/10/12.5 mg and OM/AML/HCTZ 40/10/25 mg compared to OM/AML 40/10 mg at Weeks 12 and 16 using conventional blood pressure measurement. • To evaluate the antihypertensive efficacy from baseline (Week 8) to Week 16 in daytime, nighttime, and 24-hour diastolic blood pressure (DBP) and systolic blood pressure (SBP) assessed by 24-hour ambulatory blood pressure monitoring (ABPM). • To evaluate the number (%) of subjects achieving blood pressure goal (defined as seated blood pressure <140/90 mmHg; <130/80 mmHg for subjects with diabetes,

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	chronic renal disease [defined as creatinine clearance ≥30 mL/min and ≤60 mL/min], or chronic cardiovascular disease), and blood pressure thresholds of <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, and <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg at Weeks 12 and 16. • To evaluate the safety and tolerability of OM/AML/HCTZ triple combination therapy during Weeks 8 to 16. **Periods III and IV (Week 16 to Week 32) – Objectives:** The objectives for Periods III and IV included the following: • To evaluate the antihypertensive efficacy of up-titration to OM/AML/HCTZ 40/10/25 mg in subjects not achieving blood pressure goal on OM/AML/HCTZ 40/10/12.5 mg based on changes from Week 24 to Week 32 in conventional blood pressure measurement and in daytime, nighttime, and 24-hour DBP and SBP assessed by 24-hour ambulatory blood pressure measurements (ABPM). • To evaluate the number (%) of subjects achieving blood pressure goal and blood pressure thresholds at Week 32. • To evaluate the safety and tolerability of triple combination OM/AML/HCTZ therapy during Weeks 16 to 32.
Study Design/Methodology:	**Methodology**: This was a Phase 3, randomised, double-blind, parallel-group, multicentre, multinational study with an 8-week, single-blind, run-in period (Period I), followed by an 8-week, randomised, double-blind add-on period (Period II), an 8-week, single-blind period (Period III), and an 8-week, double-blind randomised titration period (Period IV). **Screening/Taper-off Period (1 to 5 weeks)** <u>Subjects not on Antihypertensive Medications at Screening</u> To be eligible for the study, subjects not on antihypertensive medications at screening (eg, newly diagnosed subjects) had to have a mean trough SeSBP ≥160 mmHg and a mean trough SeDBP ≥100 mmHg at Visit 1. Eligible subjects returned to the clinic approximately 1 week after screening and entered Period I of the study. <u>Subjects on Antihypertensive Medications at Screening</u> To be eligible for the study, subjects who were on a stable dose of antihypertensive monotherapy for at least 4 weeks prior to screening had to have a mean trough SeSBP ≥150 mmHg and a mean trough SeDBP ≥95 mmHg at screening (Visit 1). Subjects who were on a stable dose of any combination of antihypertensive medications that included OM, AML, or HCTZ for at least 4 weeks prior to screening had to have a mean trough SeSBP ≥140 mmHg and a mean trough SeDBP ≥90 mmHg at Visit 1. Subjects who met these criteria returned to the clinic approximately 1 week after screening and entered Period I of the study.

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Subjects who were on any other combination of antihypertensive medications that did not include OM, AML, or HCTZ were required to be tapered off of their medication. Subjects were to begin the taper-off period within 3 weeks of the screening visit and were weaned from their medication over the course of 1 to 2 weeks, per sound medical judgment. At the end of the taper-off period, subjects had to have a mean trough SeSBP ≥160 mmHg and a mean trough SeDBP ≥100 mmHg in order to enter Period I of the study.

Period I (Week 0 to Week 8)

Period I was an 8-week, single-blind, run-in period in which all subjects received dual combination treatment with OM/AML 40/10 mg. On Day 1 (Visit 2), subjects who met all of the inclusion criteria and none of the exclusion criteria were dispensed OM/AML 40/10 mg. Subjects were to receive OM/AML 40/10 mg for the entire 8-week duration of Period I. Subjects who experienced symptomatic hypotension during Period I were excluded from further participation in the study.

Period II (Week 8 to Week 16)

Period II was an 8-week, double-blind, add-on treatment period. Subjects had to have a mean trough SeSBP ≥140 mmHg and a mean trough SeDBP ≥90 mmHg at the end of Period I in order to enter Period II of the study. At Visit 4 (Week 8), eligible subjects were randomly assigned in a 1:1:1 ratio to continue on OM/AML 40/10 mg, to receive OM/AML/HCTZ 40/10/12.5 mg treatment, or to receive OM/AML/HCTZ 40/10/25 mg. Subjects were to receive their randomised treatment for the entire 8-week duration of Period II.

Period III (Week 16 to Week 24)

Period III was an 8-week, single-blind treatment period in which all subjects received triple combination treatment with OM/AML/HCTZ 40/10/12.5 mg. All subjects who completed Period II were eligible to enter Period III. Subjects with a mean trough SeSBP ≥160 mmHg or a mean trough SeDBP ≥100 mmHg after at least 2 weeks of treatment in Period III could proceed directly to Period IV without completing Period III.

Period IV (Week 24 to Week 32)

Period IV was an 8-week, double-blind, titration treatment period. At the end of Period III, subjects who had not achieved blood pressure goal on OM/AML/HCTZ 40/10/12.5 mg were randomised in a 1:2 ratio to continue to receive OM/AML/HCTZ 40/10/12.5 mg or to have their dose up-titrated to OM/AML/HCTZ 40/10/25 mg. Subjects who had achieved blood pressure goal at the end of Period III continued to receive OM/AML/HCTZ 40/10/12.5 mg in Period IV.

The double-blind, titration period ended at Week 32. Following Week 32, subjects were treated at the investigator's discretion. If necessary, subjects returned for a follow-up visit 2 weeks after their last dose of study medication to assess any adverse events that were

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	ongoing at Week 32 or Early Termination.
Duration of Treatment for Individual Subject:	32 weeks
Number of Subjects:	Planned: 1965 subjects Screened: 3420 subjects Enrolled: 2204 subjects Randomised: 808 subjects Completed: 749 subjects
Diagnosis and Main Criteria for Study Entry:	This study enrolled male and female subjects 18 years or older with moderate to severe hypertension. Newly diagnosed hypertensive subjects as well as subjects on antihypertensive therapy could be included in the study.
Investigational Product and Comparator Information:	Dosage Form: OM/AML 40/10 mg film-coated tablets (modified clinical version of Sevikar®) Route of Administration: orally, once daily Lot No.: [redacted] Packaging Information: blister cards Dosage Form: HCTZ 12.5 mg tablets Route of Administration: orally, once daily Lot No.: [redacted] Packaging Information: blister cards Dosage Form: Placebo to match HCTZ 12.5 mg tablets Route of Administration: orally, once daily Lot No.: [redacted] Packaging Information: blister cards

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the change in mean trough SeDBP from baseline (end of OM/AML run-in period [Week 8]) to the end of the double-blind Period II (Week 16).

Secondary efficacy variables included the following:

- Changes in mean trough SeDBP from baseline (Week 8) to Weeks 12, 16, 24, and 32;
- Changes in mean trough SeSBP from baseline (Week 8) to Weeks 12, 16, 24, and 32 and Week 16 with LOCF;
- Changes in daytime, nighttime, and 24-hour DBP and SBP, assessed by 24-hour ABPM from baseline (Week 8) to Weeks 16, 24, and 32;
- Number (%) of subjects achieving trough seated blood pressure goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) during Period II, Period III, and Period IV;
- Number (%) of subjects achieving trough seated blood pressure thresholds (ie, <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg) during Period II, Period III, and Period IV; and
- Clinical benefit of up-titration from OM/AML/HCTZ 40/10/12.5 mg to 40/10/25 mg during Period IV in terms of conventional blood pressure and ABPM parameters.

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Safety:

Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.

Statistical Methods:

The primary efficacy variable was the change from baseline in SeDBP at the end of Period II with last observation carried forward (LOCF). Treatment comparisons were performed using an Analysis of Covariance (ANCOVA) model with baseline blood pressure as a covariate and treatment, age group (≥65 years, <65 years), and diabetic status (yes, no) as fixed effects. The differences in least-squares (LS) means between treatments are also presented.

The secondary efficacy analyses involving the change in blood pressure from baseline were performed in a similar manner.

The proportion of subjects who achieved blood pressure goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) and blood pressure thresholds (<140/90 mmHg, <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg) were summarised for each treatment group in Periods II, III, and IV. Treatment comparisons were performed using the Cochran-Mantel-Haenszel test stratified by age group and diabetic status at a 0.05 significance level.

The titration effects in Period IV were analysed by an ANCOVA model with seated blood pressure at the end of the Period III as a covariate and treatment, age group, and diabetic status as main effects.

Subgroup analyses for the change from baseline in seated blood pressure and the proportion of subjects who achieved blood pressure goal at Week 16 with LOCF was performed for age group, gender, hypertension severity, diabetic status, and body mass index (BMI) category in Period II. For each of these subgroup variables, 2-sided p-values for testing the significance of triple combination treatment against the dual combination treatment were derived from an ANCOVA model that included baseline blood pressure as a covariate and treatment as a fixed effect. The differences in LS means between treatments are also presented. For the proportion of subjects achieving blood pressure goal, comparisons between triple combinations and OM/AML 40/10 mg were performed using individual Fisher's Exact tests at a 0.05 significance level.

Safety analyses included extent of exposure, adverse events, laboratory results, vital signs, ECGs, and concomitant medications. Safety Set 1 was defined as the set of all subjects who received at least 1 dose of single-blind study medication in Period I. Safety Set 2 included all subjects who received at least 1 dose of double-blind study medication in Period II. Safety Set 3 included all subjects who entered Period IV and received at least 1 dose of double-blind study medication in Period IV. All Safety Sets were used for all safety assessments.

Summary:

Efficacy Results:

Period I (Single-Blind Period)

Treatment with OM/AML 40/10 mg during the 8-week, single-blind period resulted in a mean reduction in SeSBP of 18.1 mmHg and a mean reduction in SeDBP of 10.0 mmHg.

Period II (Baseline to Week 16 with LOCF)

Changes in Seated Blood Pressure

Table S1 presents the changes in SeSBP and SeDBP and the percentage of subjects who reached blood pressure goal during Period II.

From baseline to Week 16 with LOCF, treatment with OM/AML/HCTZ 40/10/25 mg resulted in a significantly greater mean reduction in SeSBP and SeDBP compared to OM/AML 40/10 mg. Although

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not statistically significant, treatment with OM/AML/HCTZ 40/10/12.5 mg resulted in a numerically greater mean reduction in SeSBP and SeDBP compared to OM/AML 40/10 mg. In addition, treatment with OM/AML/HCTZ 40/10/25 mg resulted in a significantly greater percentage of subjects reaching their blood pressure treatment goal compared to OM/AML 40/10 mg. Although not statistically significant, treatment with OM/AML/HCTZ 40/10/12.5 mg resulted in a larger percentage of subjects reaching their blood pressure treatment goal compared to OM/AML 40/10 mg.

Table S1. Changes in Seated Systolic and Diastolic Blood Pressures (mmHg) from Baseline to Week 16 with LOCF and Percentages of Subjects Reaching Blood Pressure Goal – Full Analysis Set 1

Treatment	N [1]	Baseline [2]	Week 16 with LOCF [3]	LS Mean Change	Trt Comparison LS Mean [4]	% Reaching BP Goal
OM40/AML10	269	147.9/93.6	139.7/87.3	-6.9*/-6.1*		24.2%
OM40/AML10/HCTZ12.5	268	148.8/93.7	138.6/86.4	-8.6*/-7.1*	-1.8/-1.0	29.5%
OM40/AML10/HCTZ25	269	148.3/93.7	136.3/84.6	-10.5*/-8.9*	-3.6*/-2.8*	41.3%*

1. N is the number of subjects with values at both time points.
2. Baseline for blood pressure was defined as the last measurement prior to the first dose of randomised study medication in Period II.
3. Week 16 with LOCF was defined as the last available measurement during Period II.
4. Treatment comparison of triple combinations vs. OM/AML/HCTZ 40/10 mg for the Full Analysis Set 1.

* Statistically significant based on $p<0.05$.
AML = amlodipine besylate; BP = blood pressure; HCTZ = hydrochlorothiazide; LOCF = last observation carried forward; LS = least squares; OM = olmesartan medoxomil; Trt = treatment.
Sources: Post-text Tables 15.2.1.1, 15.2.1.2, and 15.2.3.1

Changes in 24-Hour Ambulatory Blood Pressure

Table S2 presents the changes in 24-hour ambulatory SBP and SDP and the percentage of subjects who reached protocol-specified blood pressure goal (<140/90 mmHg for subjects without diabetes and <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) based on ambulatory blood pressure measurements during Period II.

From baseline to Week 16 with LOCF, both triple combination therapies resulted in significantly greater mean reductions in 24-hour ambulatory SBP and DBP compared to OM/AML 40/10 mg. These comparatively larger reductions in 24-hour ambulatory blood pressure resulted in greater percentages of subjects reaching their protocol-specified blood pressure treatment goal with the triple combination therapies compared to OM/AML 40/10 mg.

Table S2. Changes in 24-Hour Mean Ambulatory Systolic and Diastolic Blood Pressures (mmHg) from Baseline to Week 16 with LOCF and Percentages of Subjects Reaching Protocol-Specified Blood Pressure Goal Based on 24-Hour ABPM – Full Analysis Set 1

Treatment	N [1]	Baseline [2]	Week 16 with LOCF [3]	LS Mean Change	Trt Comparison LS Mean [4]	% Reaching BP Goal
OM40/AML10	229	130.4/79.8	127.2/78.0	-1.9*/-2.1*		68.8%
OM40/AML10/HCTZ12.5	237	130.0/80.4	123.7/76.5	-5.1*/-4.0*	-3.2*/-1.9*	77.7%*
OM40/AML10/HCTZ25	228	130.4/79.9	122.6/74.9	-6.6*/-5.3*	-4.6*/-3.2*	74.9%

1. N is the number of subjects with values at both time points.
2. Baseline for blood pressure was defined as the last measurement prior to the first dose of randomised study medication in Period II.
3. Week 16 with LOCF was defined as the last available measurement during Period II.
4. Treatment comparison of triple combinations vs. OM/AML/HCTZ 40/10 mg for the Full Analysis Set 1.

* Statistically significant based on $p<0.05$.
AML = amlodipine besylate; BP = blood pressure; HCTZ = hydrochlorothiazide; LOCF = last observation carried forward; LS = least squares; OM = olmesartan medoxomil; Trt = treatment.
Sources: Post-text Tables 15.2.2.1, 15.2.2.4, and 15.2.3.2

Period III (Week 16 to Week 24)

Subjects in the Period III Analysis Set who received OM/AML/HCTZ 40/10/12.5 mg had statistically significant mean reductions in SeSBP (-14.8 mmHg; $p<0.0001$) and SeDBP (-10.9 mmHg; $p<0.0001$) from baseline (defined as the last measurement prior to the first dose of randomised study medication in Period II) to Week 24 with LOCF. At the Week 24 with LOCF visit, 442 (56.6%) of the 781 subjects

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who were on OM/AML/HCTZ 40/10/12.5 mg were at blood pressure goal.

Period IV (Week 24 to Week 32)

Changes in Seated Blood Pressure

Table S3 presents the changes in SeSBP and SeDBP and the percentage of subjects who reached blood pressure goal during Period IV.

During Period IV, the following changes in SeSBP and SeDBP were observed:

- The group of subjects who were non-responders on OM/AML/HCTZ 40/10/12.5 mg at Week 24 and were randomised to continue on OM/AML/HCTZ 40/10/12.5 mg during Period IV had a statistically significant LS mean reductions in SeSBP and SeDBP (-5.5/-6.7 mmHg; p<0.0001) from Week 24 to Week 32 with LOCF. The group of subjects who were non-responders on OM/AML/HCTZ 40/10/12.5 mg and were randomised to OM/AML/HCTZ 40/10/25 mg during Period IV also had a statistically significant LS mean reductions in SeSBP and SeDBP (-7.8/-7.9 mmHg; p<0.0001) from Week 24 to Week 32 with LOCF. The treatment difference for mean reduction in SeSBP between the 2 non-responder groups was statistically significant (LS mean treatment difference of -2.3 mmHg; p=0.0451). The treatment difference for mean reduction in SeDBP was not statistically significant (p=0.1611).

During Period IV, the following percentages of subjects reached blood pressure goal:

- Among non-responders on OM/AML/HCTZ 40/10/12.5 mg at Week 24, up-titration to treatment with OM/AML/HCTZ 40/10/25 mg during Period IV resulted in a significantly greater percentage of subjects reaching blood pressure treatment goal at Week 32 with LOCF compared to continued treatment with OM/AML/HCTZ 40/10/12.5 mg (45.4% vs. 32.3%; p=0.0412).

Table S3. Changes in Seated Systolic and Diastolic Blood Pressures (mmHg) from Week 24 to Week 32 with LOCF and Percentages of Subjects Reaching Blood Pressure Goal – Full Analysis Set 2/Responders from Period III

Treatment	N [1]	Week 24	Week 32 with LOCF [2]	LS Mean Change [3]	Trt Comparison LS Mean [4]	% Reaching BP Goal
OM40/AML10/HCTZ12.5 responders continued on OM40/AML10/HCTZ12.5	466	126.8/78.4	126.4/78.4	-0.4/-0.0		77.7%
OM40/AML10/HCTZ12.5 non-responders randomised to OM40/AML10/HCTZ12.5	95	143.0/89.7	136.5/83.9	-5.5*/-6.7*	-2.3*/-1.2	32.3%
OM40/AML10/HCTZ12.5 non-responders randomised to OM40/AML10/HCTZ25	196	143.8/89.2	134.6/82.5	-7.8*/-7.9*		45.4%*

1. N is the number of subjects with values at both time points.
2. Week 32 with LOCF was defined as the last available measurement during Period IV.
3. Mean change presented for the group in which up-titration comparison was not made.
4. Up-titration comparison of OM/AML/HCTZ 40/10/25 mg vs. OM/AML/HCTZ 40/10/12.5 mg for the Full Analysis Set 2.

* Statistically significant based on p<0.05.
AML = amlodipine besylate; BP = blood pressure; HCTZ = hydrochlorothiazide; LOCF = last observation carried forward; LS = least squares; OM = olmesartan medoxomil; Trt = treatment.
Sources: Post-text Tables 15.2.6.1, 15.2.6.2, and 15.2.7.1

Changes in 24-Hour Ambulatory Blood Pressure

Table S4 presents the mean changes in 24-hour ambulatory SBP and DBP and the percentage of subjects who reached protocol-specified blood pressure goal (<140/90 mmHg for subjects without diabetes and <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) based on 24-hour ambulatory blood pressure measurements during Period IV.

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During Period IV, the following changes in 24-hour ambulatory DBP and SBP were observed:

- The group of subjects who were non-responders on OM/AML/HCTZ 40/10/12.5 mg at Week 24 and were randomised to continue on OM/AML/HCTZ 40/10/12.5 mg during Period IV had a non-significant LS mean reduction in 24-hour ambulatory SBP (-0.4 mmHg; p=0.8073) and a statistically significant LS mean reduction in 24-hour ambulatory DBP (-2.2 mmHg; p=0.0237) from Week 24 to Week 32 with LOCF. The group of subjects who were non-responders on OM/AML/HCTZ 40/10/12.5 mg and were randomised to OM/AML/HCTZ 40/10/25 mg during Period IV had a statistically significant LS mean reduction in SeSBP and SeDBP (-4.3/-4.4 mmHg; p≤0.0004) from Week 24 to Week 32 with LOCF. The treatment difference for mean reduction in 24-hour ambulatory SBP and DBP between the 2 non-responder groups was statistically significant (LS mean treatment difference of -4.0/-2.2 mmHg; p≤0.0253).

During Period IV, the following percentages of subjects reached protocol-specified blood pressure goal based on 24-hour ambulatory blood pressure measurements:

- Among non-responders on OM/AML/HCTZ 40/10/12.5 mg at Week 24, up-titration to treatment with OM/AML/HCTZ 40/10/25 mg during Period IV resulted in a significantly greater percentage of subjects reaching their protocol-specified blood pressure goal at Week 32 with LOCF compared to continued treatment with OM/AML/HCTZ 40/10/12.5 mg (74.3% vs. 59.3%; p=0.0268).

Table S4. Changes in 24-Hour Ambulatory Systolic and Diastolic Blood Pressures (mmHg) from Week 24 to Week 32 with LOCF and Percentages of Subjects Reaching Protocol-Specified Blood Pressure Goal Based on 24-Hour ABPM – Full Analysis Set 2/Responders from Period III

Treatment	N [1]	Week 24	Week 32 with LOCF [2]	LS Mean Change [3]	Trt Comparison LS Mean [4]	% Reaching BP Goal
OM40/AML10/HCTZ12.5 responders continued on OM40/AML10/HCTZ12.5	363	119.0/73.3	118.7/73.0	-0.3/-0.2		87.8%
OM40/AML10/HCTZ12.5 non-responders randomised to OM40/AML10/HCTZ12.5	77	131.0/80.9	129.0/79.0	-0.4/-2.2*	-4.0*/-2.2*	59.3%
OM40/AML10/HCTZ12.5 non-responders randomised to OM40/AML10/HCTZ25	158	129.9/79.7	124.4/76.2	-4.3*/-4.4*		74.3%*

1. N is the number of subjects with values at both time points.
2. Week 32 with LOCF was defined as the last available measurement during Period IV.
3. Mean change presented for the group in which up-titration comparison was not made.
4. Up-titration comparison of OM/AML/HCTZ 40/10/25 mg vs. OM/AML/HCTZ 40/10/12.5 mg for the Full Analysis Set 2.

* Statistically significant based on p<0.05.
AML = amlodipine besylate; BP = blood pressure; HCTZ = hydrochlorothiazide; LOCF = last observation carried forward; LS = least squares; OM = olmesartan medoxomil; Trt = treatment.
Sources: Post-text Tables 15.2.6.5, 15.2.6.8, and 15.2.7.2

There were small differences in how the subgroups (age, gender, hypertension severity, diabetic status, and baseline BMI category) responded to treatment with the triple combination therapies and dual combination therapy. However, none of these differences would necessitate a dosage change in any subgroup. In all subgroups where the numbers of subjects were adequate for interpretation, the reduction in seated and ambulatory blood pressures with triple combination therapies was numerically greater compared to the component dual combination therapy. Thus, the benefits observed for the overall population were similarly observed for the subgroups analysed.

Safety Results:

No new safety issues were observed when subjects were treated with triple combination therapies relative to the component dual combination therapy.

Safety Set 1 included 2203 subjects who received at least 1 dose of single-blind study medication (OM/AML 40/10 mg) in Period I. During Period I, 432 (19.6%) subjects had a TEAE and 171 (7.8%) subjects had a drug-related TEAE. Most TEAEs and drug-related TEAEs were considered mild or

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moderate in severity. The following is a summary of adverse events during Period I:

- In total, 15 (0.7%) subjects in Safety Set 1 had a serious adverse event (SAE). None of the SAEs were considered to be related to study medication.
- In total, 49 (2.2%) subjects in Safety Set 1 discontinued study medication due to a TEAE.
- In total, 38 (1.7%) subjects discontinued due to a drug-related TEAE and 6 (0.3%) subjects discontinued due to an SAE.
- One subject died during Period I. Subject 4208-0008 died from a pulmonary embolism; the investigator did not consider the event to be related to study medication.

Safety Set 2 included 806 subjects who received a least 1 dose of double-blind study medication (OM/AML 40/10 mg, OM/AML/HCTZ 40/10/12.5 mg, or OM/AML/HCTZ 40/10/25 mg) in Period II. During Period II, there were no meaningful differences in the number of subjects experiencing TEAEs, drug-related TEAEs, SAEs, or in the number of subjects who discontinued study medication due to a TEAE across the 3 treatment groups.

Table S5 summarises the adverse events during Period II for Safety Set 2.

Table S5. Overview of Adverse Events – Number (%) of Subjects – Period II – Safety Set 2

Category	OM40/ AML10 (N = 269) n (%)	OM40/ AML10/ HCTZ12.5 (N = 267) n (%)	OM40/ AML10/ HCTZ25 (N = 270) n (%)	Total (N =806) n (%)
Subjects with TEAEs				
Any TEAE	36 (13.4)	40 (15.0)	39 (14.4)	115 (14.3)
Any drug-related [1] TEAE	14 (5.2)	14 (5.2)	15 (5.6)	43 (5.3)
Maximum severity of TEAEs				
Any TEAE				
Mild	26 (9.7)	28 (10.5)	31 (11.5)	85 (10.5)
Moderate	10 (3.7)	12 (4.5)	7 (2.6)	29 (3.6)
Severe	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Drug-related [1] TEAEs				
Mild	11 (4.1)	12 (4.5)	13 (4.8)	36 (4.5)
Moderate	3 (1.1)	2 (0.7)	2 (0.7)	7 (0.9)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with SAEs during Period II				
Any SAE	2 (0.7)	1 (0.4)	2 (0.7)	5 (0.6)
Any drug-related [1] SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with AE leading to discontinuation of study medication during Period II [2]				
Any AE	4 (1.5)	2 (0.7)	3 (1.1)	9 (1.1)
Any TEAE	3 (1.1)	1 (0.4)	3 (1.1)	7 (0.9)
Any drug-related [1] TEAE	3 (1.1)	1 (0.4)	3 (1.1)	7 (0.9)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Safety Set 2 included all subjects who received at least 1 dose of double-blind study medication in Period II.
Treatment-emergent adverse events were adverse events that emerged during treatment having been absent pre-treatment, or worsened relative to the pre-treatment state. Treatment-emergent adverse events were defined as having a start date on or after the first dose of Period II study medication and up to the first dose of Period III study medication for subjects continuing into Period III, or up to and including 14 days after the last dose date of study medication in Period II for early terminated subjects.
1. Drug-related was defined as definitely, probably, or possibly related to randomised study medication.
2. Based on "action taken" on Adverse Event electronic case report form.
AE = adverse event; AML = amlodipine besylate; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Post-text Table 15.3.3.1

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-8635		
Name of Active Ingredient: olmesartan medoxomil + amlodipine besylate + hydrochlorothiazide		

The Period III Analysis Set included 782 subjects who received single-blind treatment with OM/AML/HCTZ 40/10/12.5 mg during Period III. The following is a summary of adverse events during Period III:

- In total, 99 (12.7%) subjects had a TEAE and 16 (2.0%) subjects had a drug-related TEAE; the majority of TEAEs and drug-related TEAEs were considered mild or moderate in severity;
- In total, 9 (1.2%) subjects had an SAE; none of the SAEs were considered to be related to study medication; and
- In total, 5 (0.6%) subjects discontinued study medication due to an adverse event, 4 (0.5%) subjects discontinued study medication due to a TEAE, 1 (0.1%) subject discontinued study medication due to a drug-related TEAE, and 2 (0.3%) subjects discontinued study medication due to an SAE.
- There were no deaths during Period III of the study.

Safety Set 3 included 761 subjects who entered Period IV and received at least 1 dose of study medication in Period IV: 467 subjects were responders to treatment with OM/AML/HCTZ 40/10/12.5 mg during Period III and continued to receive this treatment in Period IV, 97 subjects were non-responders to treatment with OM/AML/HCTZ 40/10/12.5 mg during Period III and were randomised to continue to receive this treatment in Period IV, and 197 subjects were non-responders to treatment with OM/AML/HCTZ 40/10/12.5 mg during Period III and were randomised to receive OM/AML/HCTZ 40/10/25 mg during Period IV. Within Safety Set 3, responder and non-responder subjects who received OM/AML/HCTZ 40/10/12.5 mg during Period IV were grouped together.

Table S6 summarises the adverse events during Period IV for Safety Set 3.

Name of Sponsor/Company: Daiichi Sankyo Europe GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Test Product: CS-8635	Volume: Page:	
Name of Active Ingredient: olmesartan medoxomil + amlodipine besylate + hydrochlorothiazide		

Table S6. Overview of Adverse Events – Number (%) of Subjects – Period IV – Safety Set 3

Category	OM40/ AML10/ HCTZ12.5 (N = 564) n (%)	OM40/ AML10/ HCTZ25 (N = 197) n (%)	Total (N = 761) n (%)
Subjects with TEAEs			
Any TEAE	86 (15.2)	43 (21.8)	129 (17.0)
Any drug-related [1] TEAE	16 (2.8)	11 (5.6)	27 (3.5)
Maximum severity of TEAEs			
Any TEAE			
Mild	69 (12.2)	33 (16.8)	102 (13.4)
Moderate	17 (3.0)	9 (4.6)	26 (3.4)
Severe	0 (0.0)	1 (0.5)	1 (0.1)
Drug-related [1] TEAEs			
Mild	14 (2.5)	10 (5.1)	24 (3.2)
Moderate	2 (0.4)	1 (0.5)	3 (0.4)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	1 (0.5)	1 (0.1)
Subjects with SAEs during Period IV			
Any SAE	2 (0.4)	1 (0.5)	3 (0.4)
Any drug-related [1] SAE	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with AE leading to discontinuation of study medication during Period IV [2]			
Any AE	4 (0.7)	1 (0.5)	5 (0.7)
Any TEAE	3 (0.5)	1 (0.5)	4 (0.5)
Any drug-related [1] TEAE	3 (0.5)	0 (0.0)	3 (0.4)
SAE	0 (0.0)	1 (0.5)	1 (0.1)

Safety Set 3 included all subjects who entered Period IV and received at least 1 dose of study medication in Period IV.
The OM/AML/HCTZ 40/10/12.5 mg group includes both responder and non-responder subjects from Period III.
Treatment-emergent adverse events were adverse events that emerged during treatment having been absent pre-treatment, or worsened relative to the pre-treatment state. Treatment-emergent adverse events were defined as having a start date on or after the first dose of Period IV study medication and up to and including 14 days after the last dose date of Period IV study medication.
1. Drug-related was defined as definitely, possibly, or probably related to randomised study medication.
2. Based on "action taken" on Adverse Event electronic case report form.
AE = adverse event; AML = amlodipine besylate; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Post-text Table 15.3.5.1

One subject died during Period IV. Subject 4009-0036 in the OM/AML/HCTZ 40/10/25 mg group had a cardio-respiratory arrest; the investigator did not consider this event to be related to study medication.

Overall, the incidence of adverse events throughout the study was very low. The most common TEAEs experienced by subjects during Period II occurred in the system organ classes infections and infestations (4.0%), general disorders and administration site conditions (2.2%), and metabolism and nutrition disorders (2.1%). The most common adverse events experienced by subjects during Period II were peripheral oedema (2.1%) and upper respiratory tract infection (1.5%). The incidence of peripheral oedema was slightly higher in the OM/AML 40/10 mg group (3.0%) compared to the OM/AML/HCTZ 40/10/12.5 mg group (1.5%) and the OM/AML/HCTZ 40/10/25 mg group (1.9%). Peripheral oedema remained the most common adverse event in Periods III and IV but the incidence was <2% during these later periods. These results are in accordance with the known safety profile of amlodipine.

There were no changes in physical examination or in the ECG findings that were unexpected across the different treatment groups.

There were no changes in laboratory parameters that signified a safety concern.

There were no safety issues identified specific to any of the subgroups assessed (age, gender, hypertension severity, and diabetic status). The trends observed in the evaluation of safety in the overall

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population were also observed in the safety analysis of subgroups.

Conclusions:

In a population of subjects with moderate to severe hypertension who were not adequately controlled on OM/AML 40/10 mg dual combination therapy, treatment with the OM/AML/HCTZ 40/10/12.5 mg and OM/AML/HCTZ 40/10/25 mg triple combination therapies reduced mean SeDBP and mean SeSBP to a greater extent compared to treatment with OM/AML 40/10 mg dual combination therapy.

- Statistically significant reductions were observed with the OM/AML/HCTZ 40/10/25 mg triple combination therapy compared to the OM/AML 40/10 mg dual combination therapy, while numerically larger mean reductions were observed with the OM/AML/HCTZ 40/10/12.5 mg triple combination therapy compared to the OM/AML 40/10 mg dual combination therapy.
- The larger mean reductions in SeDBP and SeSBP observed with both triple combination therapies resulted in a numerically greater percentage of subjects reaching blood pressure treatment goals.
- The reductions in seated blood pressure with the triple combinations were confirmed by the analysis of the 24-hour ambulatory blood pressure measurements during Period II.
- Both triple combination therapies resulted in statistically significant mean reductions in 24-hour ABPM.
- During Period IV, for subjects who had an inadequate response to OM/AML/HCTZ 40/10/12.5 mg (non-responders), increasing the HCTZ component with OM/AML/HCTZ 40/10/25 mg triple combination therapy resulted in further diastolic and systolic blood pressure reductions and an increase in the percentage of subjects reaching their blood pressure treatment goal.
- The results for ambulatory blood pressures during Period IV confirmed the additional reductions observed with the triple combinations in seated cuff blood pressure and attainment of treatment goals.
- Both triple combination therapies resulted in clinically meaningful and significantly greater mean reductions in 24-hour ambulatory DBP and SBP compared to the OM/AML 40/10 mg dual combination therapy.
- In general, the same trends in blood pressure reductions observed in the overall population were also seen in the subgroups evaluated.
- Although there were modest differences among some of the subgroups evaluated, the magnitude of the differences in blood pressure reductions would not necessitate a change to the dosing regimen for any specific subgroup.

There were no new safety concerns identified and the triple combination treatments did not cause clinically meaningful changes in any of the safety parameters compared to the corresponding dual combination therapy. Although there were slight differences in the adverse event profiles observed between some of the subgroups, the magnitude of the differences would not necessitate a change in dosing regimen for any specific subgroup.

In conclusion, a positive benefit-risk assessment was confirmed for subjects not adequately controlled on dual combination therapy that need additional therapeutic benefit offered by the triple combination therapies tested in this study.

Date of the Report: 09 February 2011