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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, Parallel-Group Study Evaluating the Efficacy and Safety of Co-Administration of Triple Combinations of Olmesartan Medoxomil, Amlodipine Besylate, and Hydrochlorothiazide Compared With the Corresponding Olmesartan-Amlodipine Combination in Subjects With Hypertension (Results of the Open-Label Titration Period: Week 18 Through Week 54) CS8635-A-E302
Phase of Development:	3
Study Period:	First subject first visit date: 27 May 2009 Last subject last follow-up date: 12 January 2011
Investigators:	See Appendix 16.1.4 for a complete list of investigators.
Study Centers:	161 investigative centres in Europe
Publication (reference):	None
Study Objectives:	Although the objectives and design of each period are included in this report, only the statistical methodology and results for subjects in the open-label period (Period VI) are presented in this report. This includes subjects who entered the open-label period after Period III (Week 18) and subjects who entered the open-label period after Period V (Week 26). The results and statistical methodology for the blinded treatment periods (Period I to Period V [Day 1 through Week 26]) are presented in the CS8635-A-E302 Double-Blind Clinical Study Report. Subjects who reached blood pressure goal (<140/90 mmHg, or <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) on Period III study medication began the open-label period at Week 18 on olmesartan medoxomil (OM)/amlodipine besylate (AML)/hydrochlorothiazide (HCTZ) 20/5/12.5 mg. Subjects who did not achieve their blood pressure goal during Period III and completed Periods IV and V began the open-label period at Week 26 on OM/AML/HCTZ 40/5/25 mg to maintain the blind of the previous periods. After 4 weeks of treatment with a starting dose of OM/AML/HCTZ 20/5/12.5 mg or 40/5/25 mg, respectively, subjects were able to have their dose up- or down-titrated at the investigator's discretion, to achieve blood pressure goals, avoid hypotension, and maintain tolerability. **Objectives**: This study consisted of 6 treatment periods: a double-blind safety run-in period (Period I), a double-blind period with dual and triple combination treatments (Period II), a single-blind period with triple combination treatment (Period III), 2 double-blind periods with different triple combination treatments (Period IV and Period V), and an open-label period (Period VI). The main objective of this study was to determine if co-administration of OM, AML, and HCTZ had a clinically significant benefit versus the respective OM and AML dual therapies in controlling blood pressure in subjects with hypertension.

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Periods I–II (Day 1 to Week 10) – Primary Objective:

The primary objective was to demonstrate that OM/AML/HCTZ triple combinations are more efficacious in lowering seated diastolic blood pressure (SeDBP) than the corresponding dual combinations of OM/AML after 10 weeks of double-blind treatment.

Periods I–II (Day 1 to Week 10) – Secondary Objectives:

The secondary objectives for Periods I–II included the following:

- To evaluate the antihypertensive efficacy for SeDBP lowering with the co-administration of various doses of the triple combination of OM/AML/HCTZ compared to the corresponding dual combinations of OM/AML after 4, 6, and 8 weeks of double-blind treatment.
- To evaluate the antihypertensive efficacy for seated systolic blood pressure (SeSBP) lowering with co-administration of various doses of OM/AML/HCTZ compared to the corresponding dual combinations of OM/AML after 4, 6, 8, and 10 weeks of double-blind treatment.
- To evaluate the number (%) of subjects reaching blood pressure goal (defined as blood pressure <140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease [defined as creatinine clearance ≥30 mL/min and ≤60 mL/min], or chronic cardiovascular disease) after 4, 6, 8, and 10 weeks of double-blind treatment.
- To evaluate the number (%) of subjects reaching blood pressure thresholds of <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg after 4, 6, 8, and 10 weeks of double-blind treatment.
- To perform exploratory evaluations of Patient Reported Outcomes (PRO) questionnaire results at baseline and Week 10.

Period III to Period VI (Week 10 to Week 54) – Objectives:

The objectives for Period III to Period VI included the following:

- To gain long-term efficacy and safety experience with administration of a sequential algorithm of triple combination treatments of OM/AML/HCTZ while treating subjects to blood pressure goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease).
- To evaluate the number (%) of subjects reaching blood pressure goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) for the triple combination therapies and blood pressure thresholds of <140/90 mmHg, <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, SeDBP <90 mmHg, and SeSBP <140 mmHg.
- To evaluate the benefit of triple combination therapy up-titration from OM/AML/HCTZ 20/5/12.5 mg to OM/AML/HCTZ 40/5/12.5 mg (Period IV) and from OM/AML/HCTZ 40/5/12.5 mg to OM/AML/HCTZ 40/5/25 mg (Period V) under randomised, double-blind, controlled conditions.

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	• To evaluate the benefit of triple combination therapy up-titration from OM/AML/HCTZ 40/5/25 mg to OM/AML/HCTZ 40/10/25 mg (Period VI) under open-label conditions. • To perform exploratory evaluations of PRO questionnaire results at Week 26 and Week 54.
Study Design/Methodology:	**Methodology**: This was a Phase 3, multicentre, multinational study with a randomised, double-blind, placebo-controlled, parallel-group portion (Periods I–II) followed by a transition (Periods III–V) to an open-label portion (Period VI). The study consisted of a screening/washout period, 6 treatment periods, and a follow-up period. **Screening/Washout (maximum of 3 weeks)** To be eligible for randomisation, all subjects had to have moderate to severe hypertension defined as a mean sitting trough cuff blood pressure of ≥160/100 mmHg (SeSBP ≥160 mmHg and SeDBP ≥100 mmHg) at 2 consecutive visits (Visits 1 and 3 for naïve subjects, and Visits 2 and 3 or Visits 2.1 and 3 for subjects washing out of antihypertensive medications), and the difference in mean SeSBP/SeDBP must have been ≤20/10 mmHg between the 2 qualifying visits. <u>Subjects Naïve to Antihypertensive Medications</u> At Visit 1, subjects naïve to antihypertensive medications who had a mean sitting trough cuff blood pressure of ≥160/100 mmHg and who met all other entry criteria, proceeded to Visit 3 within 7 days for a confirmatory blood pressure assessment. Subjects naïve to antihypertensive medications who had a mean sitting trough cuff blood pressure of ≥160/100 mmHg at both Visit 1 and Visit 3 (with a difference in mean blood pressure of ≤20/10 mmHg between the 2 qualifying visits) were eligible for randomisation at Visit 3. Subjects who had never been on antihypertensive medications or who had not been on antihypertensive medications for at least 3 weeks prior to Visit 1 were considered to be naïve subjects. <u>Subjects on Antihypertensive Medications at Screening</u> At Visit 1, subjects on antihypertensive medications at the time of screening who met all other entry criteria began a washout of these medications. The investigator determined whether subjects either immediately stopped antihypertensive medications or down-titrated antihypertensive medications over a period of time. All of these subjects had a blood pressure evaluation 7 days after their last dose of antihypertensive medication (Visit 2). If the subject had a mean sitting trough cuff blood pressure ≥160/100 mmHg at Visit 2, the subject proceeded to Visit 3 within 7 days for a confirmatory blood pressure assessment. If the subject did not have a mean sitting trough cuff blood pressure ≥160/100 mmHg at Visit 2, the subject could return in 1 week for another blood pressure evaluation (Visit 2.1). If the subject met the blood pressure criteria at Visit 2.1, the subject could return within 1 week (Visit 3) for a confirmatory blood pressure assessment.

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Subjects on antihypertensive medications at the time of screening who had a mean sitting trough cuff blood pressure ≥160/100 mmHg at both Visit 2 and Visit 3 or at Visit 2.1 and Visit 3 (with a difference in mean blood pressure ≤20/10 mmHg between the 2 qualifying visits) were eligible for randomisation at Visit 3.

Periods I–II (Day 1 to Week 10)

Period I was a 2-week double-blind safety run-in period and Period II was an 8-week double-blind treatment period. Periods I–II constituted the parallel-group controlled portion of the study. On Day 1, subjects who met all of the inclusion criteria and none of the exclusion criteria were randomised to 1 of 8 treatment groups, which reflected the treatment they were to receive during Period II. This randomisation included the treatment sequence that would be taken during Period II to reach that treatment. Arrival at each of the 8 Period II randomised treatment groups occurred by way of the 11 treatment sequences shown below.

N*	Period I (Day 1 to Week 2)		Period II (Week 2 to Week 10)
20	OM/AML/HCTZ 0/0/0 mg (20 subjects)**	→	OM/AML/HCTZ 20/5/0 mg (290 subjects)
270	OM/AML/HCTZ 20/5/0 mg (560 subjects)	→	
290		→	OM/AML/HCTZ 20/5/12.5 (290 subjects)
20	OM/AML/HCTZ 0/0/0 mg (20 subjects)**	→	OM/AML/HCTZ 40/5/0 mg (290 subjects)
270	OM/AML/HCTZ 40/5/0 mg (850 subjects)	→	
290		→	OM/AML/HCTZ 40/5/12.5 mg (290 subjects)
290		→	OM/AML/HCTZ 40/5/25 mg (290 subjects)
20	OM/AML/HCTZ 0/0/0 mg (20 subjects)**	→	OM/AML/HCTZ 40/10/0 mg (290 subjects)
270	OM/AML/HCTZ 40/10/0 mg (850 subjects)	→	
290		→	OM/AML/HCTZ 40/10/12.5 mg (290 subjects)
290		→	OM/AML/HCTZ 40/10/25 mg (290 subjects)

* N is the number of subjects assigned to each treatment sequence.
** In total, 60 subjects were planned to receive placebo in Period I. Of these 60 subjects, 20 subjects were to receive each dual combination treatment in Period II.
AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

During Period I, subjects received placebo or 1 of 3 dual OM/AML treatments (OM/AML 20/5 mg, OM/AML 40/5 mg, or OM/AML 40/10 mg) for 2 weeks. In order to assess the magnitude of the placebo effect and to ascertain that the reduction in blood pressure was not a regression to the mean, approximately 60 subjects were randomly assigned to receive placebo during Period I.

Subjects who received dual combination treatment in Period I either remained on their dual combination or added HCTZ to their treatment. Subjects who received placebo in Period I received dual OM/AML treatment

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in Period II. During Period II, subjects received either 1 of 5 triple combination treatments (OM/AML/HCTZ 20/5/12.5 mg, OM/AML/HCTZ 40/5/12.5 mg, OM/AML/HCTZ 40/5/25 mg, OM/AML/HCTZ 40/10/12.5 mg, or OM/AML/HCTZ 40/10/25 mg) or one of the 3 Period I dual combination treatments according to their randomised treatment sequence.

The distribution of subjects to the 11 treatment sequences was managed by an interactive voice response system (IVRS) based on randomisation to 1 of the 8 Period II treatment groups. Randomisation was stratified by age group (<65 years, ≥65 years), diabetic status (yes, no), and study site to provide a balanced distribution of these attributes across the 8 Period II treatment groups.

Period III (Week 10 to Week 18)

Period III was an 8-week single-blind treatment period in which all subjects received triple combination treatment with OM/AML/HCTZ 20/5/12.5 mg. Subjects with uncontrolled blood pressure (systolic blood pressure [SBP] ≥160 mmHg or diastolic blood pressure [DBP] ≥100 mmHg) after 2 weeks of treatment in Period III were eligible to have their dose up-titrated. If the investigator assessed that a subject required dose titration, the Period IV treatment assignment was obtained through IVRS. The subject then moved directly into Period IV without completing Period III. The visit at which IVRS was contacted for randomisation was considered the first visit of Period IV rather than an unscheduled visit.

Period IV (Week 18 to Week 22)

Period IV was a 4-week double-blind treatment period. At the end of Period III, subjects who had not reached blood pressure goal (blood pressure <140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) on OM/AML/HCTZ 20/5/12.5 mg were randomised in a 1:2 ratio to continue to receive OM/AML/HCTZ 20/5/12.5 mg or to have their dose up-titrated to OM/AML/HCTZ 40/5/12.5 mg. Subjects who had reached blood pressure goal at the end of Period III directly entered open-label titration (Period VI) and continued to receive OM/AML/HCTZ 20/5/12.5 mg.

Subjects were to receive their assigned treatment for the entire 4-week duration of Period IV. However, subjects with uncontrolled blood pressure (SBP ≥160 mmHg or DBP ≥100 mmHg) after 2 weeks of treatment in Period IV were eligible to have their dose up-titrated. If the investigator assessed that a subject required dose titration, the Period V treatment assignment was obtained through IVRS. The subject then moved directly into Period V without completing Period IV. The visit at which IVRS was contacted for randomisation was considered the first visit of Period V rather than an unscheduled visit.

Period V (Week 22 to Week 26)

Period V was a 4-week double-blind treatment period. At the end of Period IV, subjects who had not reached blood pressure goal on OM/AML/HCTZ 20/5/12.5 mg in Periods III and IV had their dose up-titrated to OM/AML/HCTZ 40/5/12.5 mg. Subjects who had reached

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	blood pressure goal at the end of Period IV on OM/AML/HCTZ 20/5/12.5 mg continued on this treatment in Period V. Subjects who had not reached blood pressure goal on OM/AML/HCTZ 40/5/12.5 mg at the end of Period IV were randomised in a 1:2 ratio to continue to receive OM/AML/HCTZ 40/5/12.5 mg or to have their dose up-titrated to OM/AML/HCTZ 40/5/25 mg. Subjects who had reached blood pressure goal at the end of Period IV on OM/AML/HCTZ 40/5/12.5 mg continued on this treatment in Period V. All subjects received their assigned treatments for the entire 4-week duration of Period V. **Period VI (Week 26 to Week 54)** Period VI was an open-label titration period. Subjects who did not achieve blood pressure goal at the end of Period III and went on to complete Periods IV and V received OM/AML/HCTZ 40/5/25 mg for the first 4 weeks of Period VI to maintain the blind of previous periods. Subjects who reached blood pressure goal at the end of Period III and did not participate in Periods IV and V received OM/AML/HCTZ 20/5/12.5 mg for the first 4 weeks of Period VI. After 4 weeks of treatment, subjects could, at the discretion of the investigator, have their dosage adjusted at any time in order to achieve blood pressure goal, avoid hypotension, and maintain tolerability. Subjects entering Period VI after completing Period V could have had their dose adjusted after 2 weeks of Period VI treatment for tolerability reasons. Subjects directly entering open-label titration from Period III could have had their dose adjusted during the first 4 weeks of Period VI for medical reasons. During Period VI, doses could be up- or down-titrated to the following triple combinations: • OM/AML/HCTZ 20/5/12.5 mg; • OM/AML/HCTZ 40/5/12.5 mg; • OM/AML/HCTZ 40/5/25 mg; • OM/AML/HCTZ 40/10/12.5 mg; or • OM/AML/HCTZ 40/10/25 mg. The open-label titration period ended at Week 54. Following Week 54, subjects were treated at the investigator's discretion. If a subject's SeDBP dropped to <90 mmHg or if a subject experienced signs and/or symptoms of intolerability, back- or down-titration was permitted at any time. 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 ongoing at Week 54 or Early Termination.
Duration of Treatment for Individual Subject:	54 weeks
Number of Subjects:	Planned: 2320 subjects Screened/Enrolled: 3195 subjects Randomised: 2690 subjects

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Entered the open-label period at the end of Period III (Week 18): 1837 subjects
Entered the open-label period at the end of Period V (Week 26): 672 subjects
Completed the open-label period: 2439 subjects
Discontinued the open-label period: 70 subjects

Diagnosis and Main Criteria for Study Entry:

This study enrolled male and female subjects 18 years or older with moderate to severe hypertension (defined as mean trough seated blood pressure ≥160/100 mmHg [SeSBP ≥160 mmHg and SeDBP ≥100 mmHg]). Newly diagnosed hypertensive subjects (näive subjects) as well as subjects on antihypertensive therapy could be included in the study.

Investigational Product and Comparator Information:

Dosage Form	Route of Administration	Lot Numbers	Packaging Information
OM/AML/HCTZ 20/5/12.5 mg film-coated tablets	orally; once daily	[redacted]	HDPE-bottles
OM/AML/HCTZ 40/5/12.5 mg film-coated tablets	orally; once daily	[redacted]	HDPE-bottles
OM/AML/HCTZ 40/5/25 mg film-coated tablets	orally; once daily	[redacted]	HDPE-bottles
OM/AML/HCTZ 40/10/12.5 mg film-coated tablets	orally; once daily	[redacted]	HDPE-bottles
OM/AML/HCTZ 40/10/25 mg film-coated tablets	orally; once daily	[redacted]	HDPE-bottles

AML = amlodipine besylate; HCTZ = hydrochlorothiazide;
HDPE = high-density polyethylene; OM = olmesartan medoxomil.

Criteria for Evaluation:

Efficacy variables for the open-label period included the following:

- SeDBP and SeSBP for each dosing regimen at each visit week of the open-label period;
- Changes in mean trough SeDBP and SeSBP from OM/AML/HCTZ 40/5/25 mg to OM/AML/HCTZ 40/10/25 mg during Period VI. The number of subjects reaching blood pressure goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) was also summarised for the titration step;
- Number (%) of subjects reaching trough seated blood pressure goal (<140/90 mmHg; <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular

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disease) for each dosing regimen at each visit during the open-label period; and

- Changes in PRO questionnaire results from baseline to Week 54/ET.

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

Statistical Methods:

The statistical methods described below are applicable to the open-label period only.

The Open-Label Analysis Set included all subjects who entered the open-label period at the end of Period III or after Period V and received at least one dose of study medication.

Summary statistics are presented for mean trough SeDBP and mean trough SeSBP for each dosing regimen at each visit.

Summary statistics are also presented for the titration effect corresponding to changes in dosing regimen for SeDBP and SeSBP. The titration effect was calculated as the blood pressure value at the last visit on the new dosing regimen minus the blood pressure value at the last visit of the previous dosing regimen.

The number and percentage of subjects achieving blood pressure goal (<140/90 mmHg or <130/80 mmHg for subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) at each open-label visit week were summarised by dosing regimen.

Safety analyses included extent of exposure, adverse events, laboratory results, vital signs, ECGs, and concomitant medications and were performed on the Open-Label Analysis Set.

Summary:

Efficacy Results:

In total, 2509 subjects entered the open-label period of the study. At Week 54/Early Termination (ET) by onset regimen:

- The 1448 subjects who were on OM/AML/HCTZ 20/5/12.5 mg had a mean SeDBP of 76.8 mmHg and a mean SeSBP of 124.4 mmHg.
- The 269 subjects who were on OM/AML/HCTZ 40/5/12.5 mg had a mean SeDBP of 78.7 mmHg and a mean SeSBP of 128.8 mmHg.
- The 481 subjects who were on OM/AML/HCTZ 40/5/25 mg had a mean SeDBP of 78.5 mmHg and a mean SeSBP of 129.8 mmHg.
- The 147 subjects who were on OM/AML/HCTZ 40/10/12.5 mg had a mean SeDBP of 79.9 mmHg and a mean SeSBP of 131.8 mmHg.
- The 163 subjects who were on OM/AML/HCTZ 40/10/25 mg had a mean SeDBP of 83.4 mmHg and a mean SeSBP of 135.6 mmHg.

During the open-label period, up-titration from OM/AML/HCTZ 40/5/25 mg to OM/AML/HCTZ 40/10/25 mg resulted in a mean reduction in SeDBP of 6.2 mmHg and a mean reduction in SeSBP of 11.9 mmHg.

At Week 54/ET, blood pressure goal was achieved by a total of 1959 (78.1%) subjects: 1295 (89.4%) subjects on OM/AML/HCTZ 20/5/12.5 mg, 197 (73.2%) subjects on OM/AML/HCTZ 40/5/12.5 mg, 328 (68.2%) subjects on OM/AML/HCTZ 40/5/25 mg, 81 (55.1%) subjects on OM/AML/HCTZ 40/10/12.5 mg, and 58 (35.6%) subjects on OM/AML/HCTZ 40/10/25 mg.

Of the 87 subjects who had their dose up-titrated from OM/AML/HCTZ 40/5/25 mg during the open-label period, 29 (33.3%) reached blood pressure goal at the time of the last dose of

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OM/AML/HCTZ 40/10/25 mg.

At Week 54/ET by final treatment regimen, mean change in SeDBP and SeSBP from baseline (beginning of the study) by final dosing regimen were the following:

- The 1446 subjects who were on OM/AML/HCTZ 20/5/12.5 mg had a mean reduction in SeDBP of 26.7 mmHg and a mean reduction in SeSBP of 42.8 mmHg.
- The 272 subjects who were on OM/AML/HCTZ 40/5/12.5 mg had a mean reduction in SeDBP of 24.9 mmHg and a mean reduction in SeSBP of 40.1 mmHg.
- The 480 subjects who were on OM/AML/HCTZ 40/5/25 mg had a mean reduction in SeDBP of 25.7 mmHg and a mean reduction in SeSBP of 39.9 mmHg.
- The 146 subjects who were on OM/AML/HCTZ 40/10/12.5 mg had a mean reduction in SeDBP of 24.6 mmHg and a mean reduction in SeSBP of 39.4 mmHg.
- The 164 subjects who were on OM/AML/HCTZ 40/10/25 mg had a mean reduction in SeDBP of 21.6 mmHg and a mean reduction in SeSBP of 36.5 mmHg.

For subjects who discontinued from the study and had a final dosing regimen that was not associated with a blood pressure measurement, their final dosing regimen may not be the same as the treatment associated with the Week 54/ET blood pressure measurement.

Safety Results:

During the open-label period, no new safety issues were identified with any of the triple combination treatments.

There were no meaningful differences in the percentages of subjects experiencing TEAEs, drug-related TEAEs, and serious adverse events (SAEs), or in the percentage of subjects who discontinued from the study due to an adverse event for the different treatments.

In total, 893 (35.6%) subjects had an adverse event. Across all treatments, the percentages of subjects with an adverse event during the open-label period were in a similar range between 23.7% to 29.2%.

In total, 273 (10.9%) subjects had a drug-related TEAE. Across all treatments, the percentages of subjects with a drug-related TEAE during the open-label period were in a similar range between 7.2% and 11.2%.

Across all treatments, most adverse events and drug-related adverse events were considered mild or moderate in severity.

In total, 53 (2.1%) subjects in the Open-Label Analysis Set had an SAE. Two (0.1%) subjects on OM/AML/HCTZ 20/5/12.5 mg experienced a total of 5 SAEs that were considered to be related to study medication (blood pressure decreased, dizziness, eye haemorrhage, retinal detachment, and gastritis).

In total, 23 (0.9%) subjects discontinued study medication due to an adverse event; 12 (0.5%) subjects discontinued study medication due to a drug-related TEAE that began during the open-label period.

Three (0.1%) subjects died during the open-label period of the study. All 3 deaths occurred while subjects were on OM/AML/HCTZ 20/5/12.5 mg. Subject 4002-0029 died from a pulmonary embolism. Subject 4807-0012 committed suicide by intentionally ingesting over 75 pills of study medication plus an unknown medication belonging to the subject's husband. Subject 4303-0105 died from cardiogenic shock. None of the deaths were considered to be related to study medication.

Overall, the most common adverse events experienced by subjects during the open-label period occurred in the system organ class infections and infestations (8.1%). The most commonly occurring TEAEs during the open-label period included peripheral oedema (2.1% to 3.5%),

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headache (1.2% to 2.4%), nasopharyngitis (0.4% to 2.1%), and dyslipidaemia (0.5% to 2.3%). There were no changes in laboratory parameters that signified a safety concern.

Conclusions:

The majority of hypertensive subjects were effectively titrated to blood pressure goal with OM/AML/HCTZ triple combination therapies. The titration from OM/AML/HCTZ 40/5/25 mg to 40/10/25 mg during the open-label period resulted in clinically meaningful decreases in SeDBP and SeSBP. No new safety concerns were identified with any of the triple combination therapies evaluated. The triple combinations did not cause clinically meaningful differences in any of the safety parameters assessed. Overall, long-term treatment with OM/AML/HCTZ was safe and well-tolerated. The safety profile of the triple combinations in this study was consistent with the safety profile for an angiotensin receptor blocker, a dihydropyridine calcium channel blocker, and a thiazide diuretic. In conclusion, a positive risk-benefit assessment was confirmed for the OM/AML/HCTZ triple combination therapy.

Date of the Report: 28 June 2011