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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: Sevikar®		
Name of Active Ingredient: Amlodipine besylate and Olmesartan medoxomil		

Title of Study:	Efficacy of Sevikar® compared to the combination of Perindopril/ Amlodipine on Central Arterial Blood Pressure in Patients with moderate to severe Hypertension- SEVITENSION Protocol number: DSE -SEV-02-09 EudraCT Number: 2009-012966-30
Phase of Development:	Study Phase 4
Study Period:	First subject first visit date: 06 Apr 2010 Last subject last follow-up date: 05 Nov 2012
Investigator(s):	Coordinating investigator: [redacted] For a complete list of Study investigator see Appendix 16.1.4.
Study Center(s):	Subjects were enrolled in 16 centers in Spain
Publication (reference):	Ruilope, LM, Schaefer, A. Efficacy of Sevikar® compared to the combination of perindopril plus amlodipine on central arterial blood pressure in subjects with moderate-to-severe hypertension: Rationale and design of the SEVITENSION study. Contemporary Clinical Trials 2011;32;710–6
Study Objectives/Hypothesis:	<u>Study Hypothesis</u> The hypothesis for the confirmatory statistical analysis was to demonstrate the non-inferiority of the fixed dose combination OM/AM 40/10 mg when compared to the combination of PER 8 mg plus AM 10 mg. <u>Primary Objective</u> The primary objective of the study was to show non-inferiority of OM/AM 40/10 mg (Sevikar®) compared to the combination of PER 8 mg plus AM 10 mg on the effect on absolute change in Central Systolic Blood Pressure (CSBP) from baseline (Week 0) to Final Examination (Last Observation Carried Forward (LOCF) approach). <u>Secondary Objectives</u> The secondary objectives of the study were to compare OM/AM 40/10 mg and the combination of PER 8 mg plus AM 10 mg descriptively with respect to: • Absolute changes in systolic and diastolic Ambulatory Blood Pressure Measurement (ABPM) (mean of 24h values, daytime and nighttime) from baseline (Week 0) to

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Final Examination (LOCF approach).

- Absolute changes in conventional mean sitting systolic and diastolic blood pressure (BP) measurements from baseline (Week 0) to Final Examination (LOCF approach).
- Absolute changes in CSBP from Week 12 to Final Examination (LOCF approach) in subjects with stabilized conventional mean sitting BP (i.e. subjects whose BP is < 140/90 mmHg or < 130/80 mmHg for diabetics/chronic kidney disease [CKD] at Visit 3 (week 12) and Visit 4 (week 18)), without stabilized conventional mean sitting BP and combined (with and without stabilized conventional mean BP).
- Absolute changes in conventional mean sitting systolic and diastolic BP measurements from Week 12 (observed cases [OC] approach) to Final Examination (LOCF approach) in subjects with stabilized conventional mean sitting BP, without stabilized conventional mean sitting BP and combined (with and without stabilized conventional mean sitting BP).
- Number of normalizers at Final Examination (LOCF approach) defined as conventional mean sitting BP <140/90 mmHg or < 130/80 mmHg in diabetics/CKD and according to ESC/ESH guideline, 2009 (< 140/90 mmHg).
- Number of responders at Final Examination (LOCF approach) defined as normalizers (according to the definition given in the study protocol and according to ESC/ESH guideline, 2009) or a decrease in conventional mean sitting systolic BP (SBP) by at least 20 mmHg and a decrease in conventional mean sitting diastolic BP (DBP) by at least 10 mmHg.
- To assess the relationship between mean sitting conventional SBP, CSBP, and systolic ABPM based on absolute changes from baseline (Week 0) to Week 24 (OC approach).
- To assess the relationship between mean sitting conventional DBP and diastolic ABPM based on changes from baseline (Week 0) to Week 24 (OC approach).

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	• Incidence of adverse events (AE) and AE profile during Run in Phase and separately during randomized double-blind (DB) Treatment Phase.
Study Design/Methodology:	Multi-center, balanced, parallel group (two treatment arms), randomized, DB (double dummy), non-inferiority study.
Duration of Treatment for Individual Subject:	The Run-in Phase for each subject lasted up to 4 weeks depending on previous treatment with AM. The DB Treatment Phase consisting of Phase I (4 weeks), Phase II (4 weeks), Phase III (4 weeks) and Phase IV (12 weeks) lasted 24 weeks. The total duration of the study for each participant lasted maximum 28 weeks.
Number of Subjects:	Planned: 554 enrolled / 442 randomized subjects Enrolled/Randomized: 600 subjects enrolled, 486 subjects randomized for DB treatment Completed/Discontinued: 407 subjects completed DB treatment phase, 79 discontinued
Diagnosis and Main Criteria for Study Entry:	Male and female Caucasians aged ≥ 40 years and ≤ 80 years with moderate to severe hypertension, defined by a SBP ≥ 160 and ≤ 200 mm Hg or DBP ≥ 100 and ≤ 115 mmHg for untreated subjects, SBP ≥ 140 mmHg or DBP ≥ 90 mmHg for insufficiently pre-treated subjects and SBP ≥ 130 mmHg or DBP ≥ 80 mmHg for insufficiently pre-treated diabetics/CKD (even after treatment with 10 mg AM during Run-in Phase or four weeks prior to study start) were eligible for participation. In addition, three additional risk factors were required. The number of diabetic/CKD subjects should not have exceeded 50% of the total study population. This was controlled by a close monitoring starting at the enrolment of a subject in the Run-in Phase by a subject registration fax sent from the study center to the monitor. The investigator received continuous information about the current status of the subjects already included into the study and the number of those still to be included.
Investigational Product and Comparator Information:	Dosage Form: tablets Route of Administration: oral Amlodipine 5 mg tablets (= Antacal/Mack Pfizer) Run in Visit -2, DSE Ch. –B [redacted] (Vendor Lot [redacted] Amlodipine 10 mg tablets (= Antacal/Mack Pfizer) Run in

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Visit -1, DSE Ch. –B [redacted] (Vendor Lot [redacted] l), [redacted] Treatment visit 0-4, [redacted]

Sevikar® 40/10 mg tablets (= DSE) Treatment visit 0-4 DSE Ch. –B [redacted]

Perindopril 4mg tablets (= Prenessa/ KRKA) Treatment visit 0-4, , DSE Ch. –B [redacted] (Vendor Lot [redacted]), [redacted]

HCTZ 12.5 mg tablets (= HCT 1A Pharma/ 1A Pharma) Visit 1/2, Visit 3/4, DSE Ch. –B [redacted] (Vendor Lot [redacted])

HCTZ 25 mg tablets (= HCT 1A Pharma/ 1A Pharma) Visit 2, Visit 3/4, DSE Ch. –B [redacted] (Vendor Lot [redacted]), [redacted]

Sevikar® 40/10mg placebo tablets (= DSE) Treatment visit 0-4 DSE Ch. –B [redacted]

Perindopril 4mg placebo tablets (= DSE) Treatment visit 0-4 DSE Ch. –B 3[redacted]

Amlodipine 10 mg placebo tablets (= DSE) Treatment visit 0-4 DSE Ch. –[redacted]

Packaging Information: The tablets were presented in blister cards which were packed in cartons

Criteria for Evaluation:

Efficacy:

Primary Efficacy Variable:

Absolute change in CSBP from baseline (Week 0) to Final Examination using LOCF approach. Central BP measurements were performed with the non invasive cardiovascular analysis system SphygmoCor®.

Secondary Efficacy Variable(s):

- Absolute changes in systolic and diastolic ABPM (mean of 24h values, daytime, nighttime) from baseline (Week 0) to Final Examination (LOCF approach).
- Absolute changes in conventional mean sitting systolic and diastolic BP measurement from baseline (Week 0) to Final Examination (LOCF approach).
- Absolute changes in CSBP from Week 12 to Final Examination (LOCF approach) in subjects with stabilized conventional mean sitting BP, without stabilized conventional mean sitting BP and combined (with and without stabilized conventional mean sitting BP).
- Absolute changes in conventional mean sitting systolic and diastolic BP

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measurement from Week 12 (OC approach) to Final Examination (LOCF approach) in subjects with stabilized conventional mean sitting BP without stabilized conventional mean sitting BP and combined (with and without stabilized conventional mean sitting BP).

- Number of normalizers at Final Examination (LOCF approach) defined as conventional mean sitting BP < 140/90 mmHg or < 130/80 mmHg in diabetics/CKD and according to ESC/ESH guideline 2009 (< 140/90 mmHg).
- Number of responders at Final Examination (LOCF approach) defined as normalizers (according to the definition given in the study protocol and according to ESC/ESH guideline, 2009) or a decrease in conventional mean sitting SBP by at least 20 mmHg and a decrease in conventional mean sitting DBP by at least 10 mmHg.

Pharmacokinetics/Pharmacodynamics: Not applicable

Safety:

Safety and tolerability will be addressed in terms of:

- Occurrence of AEs
- Vital signs
- Physical examination

Other: Not applicable

Statistical Methods:

Statistical Considerations:	Summary statistics were presented by treatment arm and visit and in addition by center (where appropriate). For continuous variables, the number of available observations (n), missing observations (Nmiss), mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum were provided. For categorical variables, the frequency and percentage in each category was displayed. Due to the primary study objective (non-inferiority), the Per Protocol Set (PPS) was the primary analysis set. The confirmatory statistical analyses of the primary efficacy endpoint were drawn based on PPS using the LOCF approach. The Full Analysis Set (FAS) was used to analyze all efficacy parameters (OC and LOCF approach, as far as applicable). However, all conclusions drawn from the analysis of the FAS were only considered as supportive due to the primary study objective (non-inferiority). For secondary efficacy endpoints, the focus was on the test for superiority and the results for the FAS were shown.
Primary Endpoint:	The primary objective of this study was to show the non-inferiority of OM/AM 40/10 mg when compared to PER 8 mg plus AM 10 mg with regard to the absolute change from baseline (Week 0) to the Final Examination, LOCF approach, in the primary efficacy parameter CSBP for the PPS.

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	Analysis of the primary efficacy parameter was performed using parametric analysis of covariance (ANCOVA) model with treatment as a main effect and baseline (Week 0) CSBP as covariate. The following statistical hypothesis was tested: H_0: $_{\mu}$OM/AM - $_{\mu}$PER+AM $\geq \Delta$ H_1: $_{\mu}$OM/AM - $_{\mu}$PER+AM $< \Delta$, where • $_{\mu}$OM/AM indicated the least-square mean changes from Baseline (Week 0) to Final Examination in CSBP of OM/AM 40/10 mg in the ANCOVA model • $_{\mu}$PER+AM indicated the least-square mean of changes from Baseline (Week 0) to Final Examination in CSBP of PER 8 mg plus AM 10 mg in the ANCOVA model • Δ indicated the non-inferiority margin (2 mmHg) Treatment with OM/AM 40/10 mg was declared non-inferior when compared to treatment with PER 8 mg plus AM 10 mg, if the upper limit of the two-sided 95% confidence interval (CI) for difference in least square means (OM/AM 40/10 mg – PER 8 mg plus AM 10 mg) for the absolute change from baseline in CSBP was less than 2 mmHg. If the upper limit of the 95% CI was less than 0 mmHg, it could be concluded that OM/AM 40/10 mg was superior to PER 8 mg plus AM 10 mg (according to CPMP: Points to Consider on switching between superiority and non-inferiority). To evaluate possible center effects, a sensitivity analysis was performed, extending the ANCOVA main model by center and treatment-by-center interaction as additional effects.
Secondary Endpoints:	The comparisons of absolute changes from baseline (Week 0) and from Week 12 to the Final Examination for the secondary efficacy variables were performed using parametric analysis of covariance (ANCOVA) model with treatment as a main effect and the respective baseline values as covariates. The proportions of normalizers and responders at Final Examination were compared between treatment groups using the $\chi 2$ test. If an expected number in any cell was smaller than 5, Fisher's exact test was applied. To evaluate possible center effect the analysis of normalizers and responders was done by means of an ordinal Cochran-Mantel-Haenszel test stratified by center. The descriptive analysis of treatment-emergent adverse events (TEAE) (incidences by treatment and overall) was performed separately for the Run-in phase using the SAF I and for the DB treatment phase using the SAF II.

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Summary:

Efficacy Results:

The primary objective of this study was to show the non-inferiority (one-sided, alpha = 0.025) of OM/AM 40/10 mg when compared to PER 8 mg / AM 10 mg with regard to the mean absolute change from baseline (Week 0) to the Final Examination in the primary efficacy parameter CSBP for the PPS, LOCF approach.

Using an ANCOVA model with treatment as a fixed effect and CSBP at baseline as a covariate, the least square mean (SE) for the absolute change from baseline to Final Examination in CSBP (LOCF) was -14.51 (0.83) mmHg in the OM/AM 40/10 mg group and -10.35 (0.84) mmHg in the PER 8 mg / AM 10 mg group.

- The point estimate for the difference between the OM/AM 40/10 mg group and the PER 8 mg / AM 10 mg group was -4.15 (1.18) mmHg with the two-sided 95% CI being [-6.48 mmHg; -1.83 mmHg]. The upper limit of this CI (-1.83 mmHg) was less than 2 mmHg (= non-inferiority margin). Thus, treatment with OM/AM 40/10 mg was non-inferior to treatment with PER 8 mg / AM 10 mg ($p < 0.0001$).

Similar results were seen for the **supportive analyses** on the FAS LOCF and the PPS and FAS (OC). As the 95% CI for the treatment effect also was entirely below zero, there was evidence of superiority in terms of statistical significance at the 5% level ($p < 0.05$). Thus, according to [CPMP/EWP/482/99] it was acceptable to calculate the p-value associated with a test of superiority and to evaluate whether this was sufficiently small to reject convincingly the hypothesis of no difference.

This test of superiority integrated in the ANCOVA model showed superiority of treatment with OM/AM 40/10 mg to treatment with PER 8 mg / AM 10 mg both for the FAS, LOCF as primary approach ($p < 0.0001$) and the PPS, LOCF as supportive analysis ($p = 0.0005$).

The results of the secondary efficacy variables for the FAS were consistent with the results of the primary efficacy endpoint:

- Concerning **changes in systolic and diastolic ABPM** (from baseline (Week 0) to Final Examination (LOCF approach)) analyzed using the same ANCOVA model, evidence of superiority OM/AM 40/10 mg treatment to PER 8 mg / AM 10 mg was seen for 24-hour systolic ABPM (FAS [LOCF]: $p = 0.0272$), 24-hour diastolic ABPM ($p = 0.0079$), daytime diastolic ABPM ($p = 0.0290$), nighttime systolic ABPM ($p = 0.0238$), and for nighttime diastolic ABPM ($p = 0.0359$), but not for daytime systolic ABPM ($p = 0.0907$).
- Furthermore, better treatment effects on conventional BP were seen in the OM/AM 40/10 mg group (FAS: SBP -16.49 mmHg / DBP -7.83 mmHg)

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compared to the PER 8 mg / AM 10 mg group (FAS: SBP -12.45 mmHg /DBP -5.41 mmHg). Superiority of OM/AM 40/10 mg treatment to PER 8 mg / AM 10 mg concerning absolute change from baseline to Final Examination (LOCF approach) was seen both for **mean sitting SBP** ($p = 0.0004$) and **mean sitting DBP** ($p = 0.0004$).

- The percentage of **normalizers** at Final Examination (LOCF approach) was higher in the OM/AM 40/10 mg group than in the PER 8 mg / AM 10 mg group (study protocol definition: 57.0% vs. 36.2%; ESC/ESH guideline, 2009: 75.6% vs. 57.5%) with the differences being statistically significant (protocol: $p < 0.0001$; ESC/ESH: $p < 0.0001$).
- The percentage of **responders** at Final Examination (LOCF approach) was higher in the OM/AM 40/10 mg group than in the PER 8 mg / AM 10 mg group (study protocol: 59.3% vs. 39.8%; ESC/ESH guideline, 2009: 76.0% vs. 59.3%). Regardless of the definition used the difference was statistically significant (study protocol: $p < 0.0001$; ESC/ESH: $p = 0.0002$).
- The **relationship** between conventional mean sitting SBP, CSBP, and systolic 24-hour ABPM as well as the relationship between conventional mean sitting DBP and 24-hour diastolic ABPM for the absolute change from baseline (Week 0) to week 24 (OC approach) was assessed by the Pearson correlation coefficient. For the relationship between the mean sitting SBP and CSBP, the Pearson Correlation Coefficient was 0.83652 indicating a high correlation between the two variables ($p < 0.0001$). For the relationship between the mean sitting SBP and 24-hour systolic ABPM and between mean sitting DBP and 24-hour ABPM, the Pearson Correlation Coefficients was 0.39714 and 0.45319, respectively, indicating a medium correlation between the two variables ($p < 0.0001$).

Furthermore, the results of the **exploratory efficacy variables** (FAS; LOCF approach) were in line with the findings from the primary and the secondary efficacy variables:

- **Absolute changes in CSBP from baseline** (Week 0) to Week 12 and Week 24 indicated superiority of OM/AM 40/10 mg to PER 8 mg / AM 10 mg ($p < 0.0001$).
- Superiority of OM/AM 40/10 mg to PER 8 mg / AM 10 mg was seen concerning **absolute changes in systolic and diastolic ABPM** from baseline (Week 0) to Week 24 for the 24-hour systolic and the 24-hour diastolic ABPM, nighttime systolic and diastolic ABPM, and daytime diastolic ABPM, but not for daytime systolic ABPM.

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- With regard to absolute **changes in conventional mean sitting SBP and DBP from baseline (Week 0) to Weeks 4, 8, 12, 18 and 24** a superior effect for OM/AM 40/10 mg treatment compared to PER 8 mg / AM 10 mg treatment was seen.
- For the time intervals **baseline to Final Examination** and **baseline to Week 12, the augmentation index** decreased in the OM/AM 40/10 mg group, while no change or a slight increase was seen in the PER 8 mg /AM 10 mg group. For the time interval baseline (Week 0) to Week 12, a superior effect for OM/AM 40/10 mg treatment compared to PER 8 mg / AM 10 mg treatment was seen.
- The **absolute change in CDBP [mmHg]** was analyzed exploratively for the time intervals baseline (Week 0) to Final Examination and baseline to Week 12. The results indicated a superior effect for OM/AM 40/10 mg treatment compared to PER 8 mg / AM 10 mg treatment.
- For all time intervals baseline (Week 0) to Final Examination and baseline (Week 0) to Weeks 4, 8, 12, 18 and 24, the mean sitting **pulse pressure** decreased in both treatment groups with the decrease being more pronounced in the OM/AM 40/10 mg group than in the PER 8 mg / AM 10 mg group. A superior effect for OM/AM 40/10 mg treatment compared to PER 8 mg / AM 10 mg treatment was seen for the time intervals baseline (Week 0) to Weeks 8, 12, and 18.
- Both the percentage of **normalizers** and the percentage of **responders** (both using the protocol and the ESC/ESH guideline, 2009 definition) was higher in the OM/AM 40/10 mg group than in the PER 8 mg / AM 10 mg group at all visits (Weeks 4, 8, 12, 18, and 24), regardless of definition used. The difference was statistically significant ($p < 0.05$) for all visits except for Week 18 (both definitions for normalizers and ESC/ESH guideline, 2009 definition for responders).

There was a certain variability in the results **by center**. However, for almost all centers, except for one with a lower number of recruited subjects (center 2), the point estimate for the difference in change CSBP between the two treatment groups was below zero, indicating a more pronounced decrease in CSBP in the OM/AM 40/10 mg group compared to the PER 8 mg / AM 10 mg group. To evaluate possible center effects, a sensitivity analysis was performed, extending the ANCOVA main model by center and treatment-by-center interaction as additional effects.

- An influence was seen for center (PPS: $p = 0.0184$; FAS $p = 0.0278$), but not for treatment-by-center interaction (PPS: $p = 0.9404$; FAS: $p = 0.3134$). The

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results of the secondary efficacy variables were consistent with this.

When analyzing the PPS, in most cases similar results to those obtained for the FAS were seen.

Subgroup analyses were performed for gender, age and BMI.

- Gender: The point estimate (95% CI) for the difference in the primary efficacy variable for the difference between the OM/AM 40/10 mg group and the PER 8 mg / AM 10 mg group was -3.66 mmHg ([-6.12,-1.20]) in male subjects and -5.78 mmHg ([-11.65,0.09]) in female subjects.
- Age: The point estimate (95% CI) for the difference in the primary efficacy variable for the difference between the OM/AM 40/10 mg group and the PER 8 mg / AM 10 mg group was -4.94 mmHg ([-7.97,-1.91]) in non-elderly subjects (< 65 years at Basic examination) and -2.83 ([-6.47,0.81]) mmHg in elderly subjects (≥65 years at basic examination).
- BMI: The point estimate (95% CI) for the difference in the primary efficacy variable for the difference between the OM/AM 40/10 mg group and the PER 8 mg / AM 10 mg group was -2.09 mmHg ([-5.56,1.38]) in non-obese (BMI < 30 kg/m^2) and -5.30 ([-8.44,-2.16]) mmHg in obese subjects (BMI ≥ 30 kg/m^2).

The respective upper limits of the two-sided 95% CIs were less than 2 mmHg (= non-inferiority margin) in all subgroups.

As further secondary endpoint the absolute changes in CSBP from Week 12 (OC approach) to Final Examination (LOCF approach) were analyzed in subjects in the **FAS-STAB**, the **FAS-NON-STAB** and the FAS. The values tended to increase in the FAS-STAB and to decrease in the FAS-NON_STAB. In all three analysis sets, the 95% CI included zero and the p-values were > 0.05. Superiority of OM/AM 40/10 mg treatment to PER 8 mg / AM 10 mg was not seen for the change in CSBP between Week 12 and Final Examination.

Similarly, when analyzing absolute changes in conventional mean sitting SBP and DBP from Week 12 (OC approach) to Final Examination, superiority of OM/AM 40/10 mg treatment to PER 8 mg / AM 10 mg was not seen for the changes in CSBP between Week 12 and Final Examination.

Safety Results:

During the Run-in phase, a total of 96 subjects out of 544 (17.6%) had at least one TEAE, including laboratory TEAE, and 53 subjects (9.7%) had at least one drug-related TEAE. One subject was reported with an SAE unrelated to AM.

During the DB treatment phase 239 out of 485 subjects (49.3%) reported at least one

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TEAE including laboratory TEAE. The percentage of subjects with TEAEs (51.2% vs. 47.3%) and the percentage of subjects who interrupted intake of study drug due to TEAE (4.1% vs. 0.8%) was somewhat higher in subjects receiving OM/AM 40/10 mg than in subjects receiving PER 8 mg / AM 10 mg. No other major differences were seen between the two treatment groups. About one quarter of subjects (25.4%) reported drug-related TEAEs. SAEs were reported for 8 subjects (1.6%). None of these were considered drug-related. Severe TEAEs occurred in 11 subjects (2.3%) and TEAEs leading to permanent discontinuation were documented in 37 subjects (7.6%). Of these, 32 subjects (6.6%) had drug-related TEAEs. No subject died during this study.

Overall and in the OM/AM 40/10 mg treatment group, TEAEs occurred most frequently in the system organ classes (SOCs) ‘general disorders and administration site conditions’ (overall: 20.0%; OM/AM 40/10 mg: 19.7%), ‘infections and infestations’ (overall: 12.2%, OM/AM 40/10 mg: 13.1%) and ‘musculoskeletal and connective tissue disorders’ (overall: 7.6%, OM/AM 40/10 mg: 9.4%), while in the PER 8 mg / AM 10 mg treatment group TEAEs occurred most frequently in the SOCs ‘general disorders and administration site conditions’ (20.3%), followed by ‘infections and infestations’ (11.2%) and ‘respiratory, thoracic and mediastinal disorders’ (7.5%).

Overall, at the preferred term (PT) level, the most common TEAEs were ‘oedema peripheral’ (18.1%), followed by ‘nasopharyngitis’ (5.2%) and ‘cough’ (4.3%). In the OM/AM 40/10 mg group ‘oedema peripheral’ (18.4%) were followed by ‘nasopharyngitis’ (4.5%) and in the PER 8 mg / AM 10 mg group ‘oedema peripheral’ (17.8%) by ‘cough’ (6.6%) and ‘nasopharyngitis’ (5.8%). The PT ‘cough’ (difference > 3 percentage points) was more common in the PER 8 mg / AM 10 mg group than in OM/AM 40/10 mg. Other than that no major differences were seen between the two treatment groups.

A total of eight subjects (1.6%) experienced serious TEAEs during the DB treatment phase, four in the OM/AM 40/10 mg group (PTs: pseudarthrosis ,joint dislocation, fall and upper limb fracture, hepatic neoplasm malignant) and four in the PER 8 mg / AM 10 mg group (PTs: respiratory tract infection, breast cancer female, acute coronary syndrome, lower gastrointestinal haemorrhage). All events were single cases. None of these serious TEAEs was drug-related.

Most frequently, subjects experienced TEAEs with a maximum severity of mild (32.2%), followed by moderate TEAEs (14.8%). Only a small percentage of subjects had TEAEs of severe intensity (2.3%). Of the 11 subjects with a maximum severity of severe, six were in the OM/AM 40/10 mg group and five were in the PER 8 mg / AM 10 mg group

For 37 subjects (7.6%) overall (18 subjects [7.4%] in the OM/AM 40/10 mg group and

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19 subjects [7.9%] in the PER 8 mg / AM 10 mg group), TEAEs led to discontinuation of study medication during the DB treatment phase.

The most common SOCs leading to discontinuation during the DB treatment phase were 'general disorders and administration site conditions', and 'respiratory, thoracic and mediastinal disorders'. At the PT level, the most common TEAE leading to discontinuation of study drug was 'oedema peripheral', followed by 'cough'. The PT 'cough' leading to discontinuation was reported for 4 subjects (1.7%) in the PER 8 mg / AM 10 mg compared to none of the subjects in the OM/AM 40/10 mg treatment group.

Pharmacokinetic/Pharmacodynamic Results: Not applicable

Other Results: Not applicable

Conclusions:

Non-inferiority as well as superiority of the treatment with OM/AM 40/10 mg compared to treatment with PER 8 mg plus AM 10 mg was shown concerning the primary efficacy variable mean absolute change in CSBP from baseline (Week 0) to the Final Examination. These results were confirmed by the results of the secondary efficacy variables.

In addition to this, OM/AM 40/10 mg was a safe and well tolerated treatment and no new safety concerns were identified in this study.

Date of the Report: 04 June 2013