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REPORT SYNOPSIS

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

Title of Study:	Effect of Olmesartan Medoxomil on Vascular Markers in Hypertensive Patients with Metabolic Syndrome (VAMOS), Protocol no. DSE 866/46 . EUDRACT Number: 2007-003130-41
Phase of Development:	3b
Study Period:	First subject first visit date: 13 October 2008 Last subject last follow-up date: 03 December 2010
Investigator(s):	[redacted]
Study Center(s):	Monocenter study: University Erlangen-Nürnberg, Krankenhausstr. 12, 91054 Erlangen
Publications (reference):	U. Raff et al. 2011 [1]
Study Objectives:	
Primary:	The primary study objective was to investigate the anti-inflammatory effect of olmesartan medoxomil (OM) 80 mg compared to OM20 and amlodipine (AML) 5 mg on the change in levels of the inflammatory marker hs-CRP.
Secondary:	The secondary study objectives were • to evaluate the additional antihypertensive efficacy in blood pressure (BP) lowering, assessed by conventional BP measurement and 24-h ambulatory BP monitoring (24-h ABPM) • to evaluate the effect on albumin excretion / microalbuminuria • to evaluate the effect on other inflammatory markers: TNF-α, IL-6, as well as on plasma 8-isoprostane 15(S)-8-iso-prostaglandin F2a concentration for oxidative stress • to evaluate the effect on insulin resistance: adiponectin, HbA1c and HOMA model • to evaluate the effect on augmentation index and pulse wave velocity as assessed with the SphygmoCor® device • to evaluate the safety and tolerability of OM and AML.
Study Design/Methodology:	This was a single-center, randomized, double-blind, cross-over, active-controlled study with 3 treatment arms After a 6-week run-in phase, patients were treated sequentially for 6 weeks each with OM20, OM80, and AML 5 mg in a randomized order, in a threefold crossover design. The study was concluded with a 3-week follow-up period without treatment.

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Duration of Treatment for Individual Subject:	The duration of the treatment period was 18 weeks, and the total study duration was 23-27 weeks for each patient.
Number of Subjects:	Planned: 60 subjects Enrolled*:* 146 subjects Randomized*:* 73 subjects Completed: 64 subjects Discontinued: 9 subjects Completers were subjects who completed all periods of the trial.

Diagnosis and Main Criteria for Study Entry:

Diagnosis: Subjects with hypertension, metabolic syndrome, and modest inflammation

Inclusion Criteria:

1. Male or female, average European outpatients ≥ 18 years old.
2. Hypertension, metabolic syndrome, and modest inflammation. At baseline, patients had to have:
   - blood pressure ≥ 130/85 mmHg, AND
   - hs-CRP ≥ 1.0 and < 10.0 mg/l

   AND at least two of the following traits of the metabolic syndrome (ATP III criteria):
   - abdominal obesity: waist circumference > 102 cm for men and > 88 cm for women
   - triglyceride level ≥ 150 mg/dl
   - HDL < 40 mg/dl for men and < 50 mg/dl for women
   - fasting blood glucose ≥ 110 mg/dl.
3. Written Informed Consent

Exclusion Criteria:

1. Insulin-dependent diabetes or type-1 diabetes.
2. Severe or resistant hypertension, or SBP > 180 mmHg and/or DBP > 110 mmHg.
3. Patients with secondary hypertension of any etiology.
4. Any acute or chronic inflammatory disease.
5. Constant use of lipid-lowering agents .
6. Patients with serious medical disorders
7. Patients with a history of cardiovascular and cerebrovascular events within the last 6 months.
8. Patients with clinically significant abnormal laboratory values.
9. Impaired hepatic function.
10. Impaired renal function.

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11. Females who are pregnant or plan a pregnancy during the time of the trial, are nursing or are of childbearing potential and not using adequate and highly effective methods of contraception.
12. Patients with a history of alcohol and/or drug abuse.
13. Patients unwilling or unable to tolerate discontinuation of their previous medication.
14. Patients who have donated 450 ml or more blood during the last three months before screening.
15. Patients who have received treatment with any investigational product within the last 30 days prior to study entry.
16. Patients unwilling or unable to provide informed consent.
17. Subjects unlikely to comply with protocol
18. Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study.
19. History of hypersensitivity to the investigational products or to drugs with similar chemical structures.
20. Patients with contraindication to OM and/or AML.
21. Subject is staff or relative of staff directly involved in the conduct of the protocol.
22. Likelihood of requiring treatment during the study period with drugs not permitted by the clinical study protocol

Investigational Product and Comparator	Olmesartan 80 mg (OM80)	Olmesartan 20 mg (OM20)	Amlodipine 5 mg (AML)
Active agent:	Olmesartan medoxomil	Olmesartan medoxomil	Amlodipine besilate
Drug form:	Film-coated Tablet	Film-coated Tablet	Tablet
Route of administration:	Oral	Oral	Oral
Dosage:	80 mg (2 tablets of 40 mg)	20 mg	5 mg
Batch No:	[redacted]		
Placebo:	Matching placebo	Matching placebo	Matching placebo
Active agent:	n.a.	n.a.	n.a.
Drug form:	Film-coated Tablet	Film-coated Tablet	Tablet
Route of administration:	Oral	Oral	Oral
Dosage:	2 tablets	1 tablet	1 tablet

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Batch No: [redacted]

Criteria for Evaluation:

Efficacy

The primary efficacy endpoint was the change in levels of the inflammatory markers hs-CRP after 6 weeks of double-blind treatment.

Secondary efficacy variables were:

- Change in trough sitting BP assessed by conventional BP measurement and the change in 24-h ABPM after 6 weeks of double-blind treatment.
- Change in the urinary-albumin-creatinine ratio (UACR) after 6 weeks of double-blind treatment.
- Change in other inflammatory markers after 6 weeks of double-blind treatment: TNF-α, IL-6, as well as on plasma 8-isoprostane 15(S)-8-iso-prostaglandin F2a concentration for oxidative stress
- Change in metabolic parameters of insulin resistance after 6 weeks of double-blind treatment: adiponectin, HbA1c and HOMA index
- Change in augmentation index and pulse wave velocity (assessed with the SphygmoCor® device) after 6 weeks of double-blind treatment.

Safety

The primary safety endpoint was the adverse event profile of OM80 and OM20 as compared to AML 5 mg. Furthermore, vital signs, 12-lead ECG, physical examination, clinical hematology, biochemistry and urinalysis were evaluated during the study.

Statistical Methods:

Presentation of Data and Analysis of Baseline Data:

Assessments made at the Screening Visit were summarized for the Safety Analysis set, the Full Analysis Set and the Per-Protocol Analysis Set. These assessments included demographic characteristics, medical history and other relevant assessments.

Confirmatory Analysis of Primary Efficacy Criterion:

The primary efficacy variable was the change from baseline in level of the inflammatory marker hs-CRP after 6 weeks of double-blind treatment.

The primary analysis was performed on the FAS (LOCF). The following three hypotheses were tested in a hierarchical order:

(1) H0: μ OM80 - μ OM20 = 0 versus H1: μ OM80 - μ OM20 $\neq$ 0

(2) H0: μ OM80 - μ AML = 0 versus H1: μ OM80 - μ AML $\neq$ 0

(3) H0: μ OM20 - μ AML = 0 versus H1: μ OM20 - μ AML $\neq$ 0

An analysis of variance (ANOVA) model with Sequence, Treatment, Period as factors and subject nested within Sequence as random effect was performed on the changes in the inflammatory marker hs-CRP after 6 weeks of double-blind treatment. The ANOVA included the calculation of

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least-square means (LSM) and the differences between treatment LSM including two-sided 95%-confidence intervals.

The primary analysis was to be repeated for the FAS (OC) and the PPS (in the case of a relevant difference in the number of subjects when compared to the FAS).

Analysis of Secondary Efficacy Criteria:

Descriptive statistics were performed for all secondary endpoints. Exploratory analyses were performed for selected secondary endpoints using the same analytical methods as described for the primary efficacy endpoint.

Continuous variables were summarized using the following descriptive statistics: number of observations, mean, standard deviation, minimum, median and maximum. Categorical measures were summarized by means of absolute and relative frequencies (counts and percentages). In general, all data was listed, sorted by subject and study period and, where appropriate, by visit.

For treatment differences the mean differences including the 95% confidence intervals were presented graphically (fishbone plot) for all efficacy variables.

Safety Analysis:

Safety and tolerability were addressed in terms of occurrences of AEs, of treatment emergent AEs (TEAEs), changes in vital signs (BP/PR), ECGs, physical examination findings, and laboratory parameters.

All TEAEs were tabulated by primary system organ class (SOC) and preferred term (PT) presenting the number of AEs and the number and percentage of subject reporting AEs.

Descriptive comprehensive data summaries, both overall and by treatment group, were produced for vital signs, ECG, physical examination and laboratory parameters. No formal statistical hypothesis testing was performed on safety and tolerability data.

Summary:

Efficacy Results: For better understanding of the results presented below, please note that the descriptive evaluations of all changes from baseline refer to unadjusted means, whereas the exploratory analyses were performed using least-squares means.

Evaluation of the Primary Efficacy Endpoint hs-CRP:

The primary efficacy variable was the absolute change from baseline (Visit 3 / Week 0) in the level of the inflammatory marker hs-CRP after 6 weeks of double-blind treatment, (LOCF approach)

No statistically significant differences were found for any of the treatments between baseline and Week 6, and no statistically significant differences were found between treatments (all $p > 0.50$). Thus, the three

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primary hypotheses were rejected.

Absolute Change from Baseline to Week6 in hs-CRP, full analysis set – descriptive statistics, LOCF approach

Week	**Treatment**	**N**	**Mean**	**SD**
Week 0 (BL)	OM80	64	3.567	2.0675
	OM20	61	3.524	2.0884
	AML	65	3.508	2.0630
Week 6 (LOCF)	OM80	64	3.412	2.0922
	OM20	61	3.507	2.3114
	AML	65	3.536	2.2738
Change Week 6 – Baseline	OM80	64	-0.156	1.4845
	OM20	61	-0.017	1.4638
	AML	65	0.027	1.5406

Absolute Change from Baseline to Week6 in hs-CRP, full analysis set – Analysis of Variance, LOCF approach

Treatment (comparison)			**Results of ANOVA model**				
					95% CI (2-tail)		
T1	**-**	**T2**	**N**	**LS-Mean**	**Lower**	**Upper**	**Pr > |t|**
OM80	-	Baseline	64	-0.078	-0.346	0.189	0.5634
OM20	-	Baseline	61	-0.048	-0.327	0.230	0.7312
AML	-	Baseline	65	0.027	-0.238	0.293	0.8393
OM80	-	OM20		-0.030	-0.418	0.358	0.8791
OM80	-	AML		-0.106	-0.484	0.272	0.5810
OM20	-	AML		-0.076	-0.459	0.308	0.6963

Secondary Efficacy Endpoints:

Sitting SBP and DBP:

Mean sitting SBP was reduced from baseline to Week 6 by 17.3 mmHg under treatment with OM80, by 14.6 mmHg under treatment with OM20, and by 12.4 mmHg under treatment with AML; p-values for all three treatments were <0.0001, and there was a statistically significant difference in sitting SBP reduction between OM80 and AML (p=0.0045).

Similar observations were made for the absolute reduction of mean sitting DBP from baseline until Week 6: Mean sitting DPB was reduced by 10.9 mmHg under treatment with OM80, by 8.5 mmHg under treatment with OM20, and by 5.7 mmHg under treatment with AML in the full analysis set; p-values for the absolute reduction from baseline for all three treatments were <0.0001. There were statistically significant differences between OM80 and OM20 (p=0.0237) as well as OM20 and AML

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(p=0.0120), and a highly significant difference between OM80 and AML (p<0.0001).

Reduction of sittin SBP and DBP frome baseline to Week 6, full analysis set, LOCF approach, exploratory analysis

	Treatment	N	Mean	SD
Sitting SBP, Change Week 6 – Baseline	OM80	69	-17.3	12.77
	OM20	68	-14.6	14.73
	AML	69	-12.4	11.49
Sitting DBP, Change Week 6 – Baseline	OM80	69	-10.9	8.73
	OM20	68	-8.5	8.67
	AML	69	-5.7	8.97

Ambulatory BP measurements:

A similar pattern was also observed for ambulatory BP measurements (ABPM): All treatments were able to lower 24h ambulatory BP considerably and significantly, but with a clear signal in favor of OM80 over AML.

Ambulatory BP measurements, full analysis set, descriptive statistics, LOCF approach

Measurement	Treatment	N	Mean	SD
24-hour SBP	OM80	31	-11.7	12.70
	OM20	26	-9.3	9.96
	AML	31	-5.2	9.66
Daytime	OM80	31	-12.3	13.56
	OM20	26	-9.4	10.16
	AML	31	-6.0	9.62
Nighttime	OM80	30	-10.7	13.46
	OM20	25	-10.3	11.09
	AML	30	-3.5	14.08

All treatments led to a clinically relevant and statistically significant decrease of 24h ambulatory SBP, but with a clear signal in favor of OM80 (p<0.0001) over AML(p=0.0105). Recent evidence suggests that specifically nighttime BP is a strong predictor of cardiovascular risk [2]. In view of this evidence, it is interesting that OM80 had the strongest effect on nighttime SBP, with a statistically highly significant difference to AML which did not have significant influence on nighttime ambulatory SBP at all (with mean absolute reductions of 10.7 mmHg for OM80 (p<0.0001), 10.3 mmHg for OM20 (p=0.0044), and 3.5 mmHg for AML (p=0.0541)). The 24-hour, daytime, and nighttime ambulatory SBP in the full analysis set, using the LOCF approach, changed significantly

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from baseline to week 6 in all treatments, except for nighttime ambulatory SBP during AML treatment.

In parallel to ambulatory SBP, mean 24-hour ambulatory DBP was reduced significantly from baseline to Week 6 during all treatments ($P<0.0001$ for OM80 and OM20; $p=0.0126$ for AML). Similar results were also found for daytime ABPM DBP. However, nighttime ambulatory DBP was significantly reduced only during both OM treatments ($p<0.0001$ for OM80; $p=0.0002$ for OM20), but not during treatment with AML ($p=0.132$). When ambulatory DBP assessments were compared between treatments in the full analysis set, using the LOCF approach, statistically significant differences in the absolute reduction of 24h, daytime and nighttime DBP from baseline to Week 6 were only found between OM80 and AML ($p=0.0007$), but neither between the OM80 and OM20 nor between the OM20 and AML treatments

Central BP Measurements:

In parallel to all other blood-pressure assessments, central SBP decreased significantly from baseline to Week 6 during all treatments ($p<0.0001$). However, there was only a significant difference between OM80 and AML, and not between the other treatments ($p=0.0117$). Pulse pressure also decreased significantly ($p<0.0001$) during all treatments, but there were no significant differences between treatments.

Urine Albumin-Creatinine Ratio:

There was a significant absolute reduction from baseline to Week 6 in the urinary-albumin-creatinine ratio in all treatments, both in the full analysis set and in the per-protocol set, but there were no significant differences between groups.

Inflammatory Markers TNF-alpha, IL-6

There were statistically significant increases in TNF-α during treatment with OM80 ($p=0.0005$) and OM20 ($p=0.0155$), but these changes were not considered clinically relevant. TNF-α did not change during treatment with AML.

There was no statistically significant absolute change from baseline to Week 6 in IL-6 during OM80 and AML treatment, but a statistically significant change from baseline in IL-6 was found for OM20; this change was not clinically relevant. There were no differences in IL-6 between treatments, and the changes from baseline were not considered to be clinically relevant.

Adiponectin, HOMA, HbA1C

There were no statistically or clinically significant changes in adiponectin values or the HOMA index from baseline to Week 6 in any of the treatments, and no differences between treatments.

An increase in HbA1C was observed from baseline to Week 6 during

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OM20 (p=0.0011) and OM80 (p=0.0242) treatment in the double-blind period using the LOCF approach which was not statistically significant for the full analysis set, but for the per-protocol set. HbA1C did not change statistically significantly from baseline to Week 6 during AML treatment. No differences were found in the statistical comparison between OM80 and OM20, as well as OM80 and AML, but there was a statistically significant difference in the HbA1C change from baseline to Week 6 between OM20 and AML (p=0.0396) in the per-protocol set, but not in the full analysis set. None of these changes were deemed clinically relevant.

Pulse Wave Velocity and Augmentation Index:

Pulse wave velocity decreased statistically and clinically significantly from baseline to Week 6 during treatment with OM80 (p=0.0088) and OM20 (p=0.0362); it also decreased during AML (p=0.2065) treatment, but this decrease was neither statistically nor clinically significant, and there were no differences between treatments.

The augmentation index decreased statistically and clinically significantly from baseline to Week 6 during all treatments (p<0.0001), but there were no differences between treatments.

Body weight, BMI, and Waist Circumference:

There were no statistically or clinically significant changes in body weight, and accordingly, BMI from baseline to Week 6 during treatment with AML or OM80, but there was statistically significant but not clinically relevant mean weight gain of 0.38 kg during treatment with OM20 (p=0.0164). This was reflected in the BMI which also slightly but not clinically significantly increased by 0.12 kg/m² during treatment with OM20 (p=0.0183). However, these changes were considered not to be clinically relevant. There were no statistically significant differences between treatments.

There was a decrease in waist circumference in the per-protocol set by 0.8 cm during treatment with OM20 which was mainly attributable to a larger mean decrease of waist circumference in DB period 3 (of 2.5 cm), but this change was not considered to be clinically relevant. In addition, abdominal obesity did not change in 90% of the patients during any of the treatments, but 10% of all subjects changed from “abdominal obesity” to “no abdominal obesity” during treatment.

ADMA, Homoarginine, NMMAS and other Markers:

Asymmetric dimethylarginine (ADMA), homoarginine, L-arginine, L-NG-monomethyl arginine citrate (L-NMMA), methyl peroxidase (MPO), and symmetric dimethylarginine (SDMA) were also assessed, and there were slight changes from baseline to Week 6 in most of these parameters for OM20 treatment, but these changes were not clinically relevant. Insulin did not change from baseline in any of the treatments.

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Exploratory Analysis of patients with hs-CRP either > 3.0 mg/L or ≤ 3.0 mg/L:

An exploratory analysis was performed for subgroups of subjects with baseline hs-CRP either > 3.0 mg/L or ≤ 3.0 mg/L. In subjects with hs-CRP ≤ 3.0 mg/L, compared to baseline, treatment with OM80 led to a statistically significant increase of mean hs-CRP of 0.376 mg/L (p=0.0173), and treatment with AML led to a statistically significant increase of mean hs-CRP by 0.431 mg/L (p=0.0042), but there were no statistically significant differences between groups, and there was no statistically significant change from baseline under treatment with OM20. Mean hs-CRP tended to increase during all treatments in subjects with hs-CRP ≤ 3.0 mg/L, and tended to decrease compared to baseline in all subjects with hs-CRP > 3.0 mg/L.

Exploratory Analysis of Isoprostane Levels:

An exploratory analysis was performed on isoprostane levels as inflammatory markers. In the FAS, a slight increase from baseline to Week 6 was found for isoprostane under OM20 treatment (p=0.0471) and under AML treatment (p=0.0098) but not under treatment with OM 80 (p=0.08136). When comparing the 3 treatment groups, there was a trend (p=0.0951) in favor of OM 20 when compared to AML. Possibly, treatment with OM80 could prevent the increase in isoprostane as a marker of oxidative stress, as this different pattern between OL80 and AML occurred in parallel to a better blood pressure reduction with OM 80.

Efficacy Conclusions:

In conclusion, neither OM nor AML had any clinically or statistically significant effect on hs-CRP. Although there was a slight decrease in hs-CRP from baseline to Week 6 during treatment with OM80, this difference was neither clinically meaningful nor statistically significant.

However, OM80 had a significantly stronger BP-lowering potential than AML, and contrary to AML, both OM doses were able to lower nighttime ambulatory SBP and DBP.

All treatments significantly lowered UACR, but only OM80 and OM20 had a statistically and clinically significant influence on pulse wave velocity.

Regarding the effects of OM in comparison to AML on markers of obesity, endothelial function, inflammation and diabetes, as well as arterial stiffness, no clear conclusions can be drawn from the results of this study.

Safety Results: Of the 73 subjects included in the safety population, 66 (90.4%) had at least one TEAE, and the TEAEs were drug-related in 33 subjects (45%).

The largest number of TEAEs (82) occurred during treatment with AML,

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	71 TEAEs were observed during treatment with OM80, and 58 TEAEs were reported during treatment with OM20. Also, less drug-related TEAEs were reported under treatment with OM20 (12) than during AML treatment (30) and OM80 treatment (25). This also applied to the number of subjects experiencing TEAEs: During OM20 treatment (37 subjects), less subjects experienced TEAEs than under treatment with OM80 and AML (45 and 48 subjects, respectively). However, no statistical significance tests were performed with regard to differences in the frequency of TEAEs between treatments (see Table 10.5). With the exception of two severe TEAEs (1 during OM20 and 1 during OM80 treatment), all TEAEs were mild to moderate in intensity. The severe TEAEs were not related to study drug. Only two subjects experienced serious TEAEs (both during treatment with OM20), none of which were drug-related, and 6 subjects discontinued due to TEAEs. The most common drug-related TEAE in this study which occurred 11 times (15.1% of patients) was headache, followed by 5 cases of peripheral edema (6.8% of patients), and 4 cases each of dizziness and vertigo (5.5% of patients, each). All other TEAEs occurred less frequently. Drug-related TEAEs were distributed evenly across treatment sequences; only peripheral edema (5 of 5 cases) and dizziness (3 of 4 cases) occurred more frequently in patients treated with AML than during OM treatment which is in line with the known safety profile of AML. There were no clinically relevant changes over time or differences between treatments in laboratory assessments, vital signs, ECG, or physical examinations. A slight decrease in blood hemoglobin and changes from negative to positive values were observed for glucose and protein in urine in all groups during treatment. However, these changes were not considered to be clinically relevant In summary, all study treatments were safe and well tolerated which corresponds to the known good safety profiles of olmesartan medoxomil and amlodipine.
Pharmacokinetic/ Pharmacodynamic Results	: No pharmacokinetic or pharmacodynamic assessments were performed in this study.
Conclusions:	• An effect of Olmesartan Medoxomil on hs-CRP could not be found. • All treatments lowered sitting BP significantly compared to baseline, whereas, OM 80 mg demonstrated a statistically significantly stronger BP lowering potential compared to AML • All treatments led to a clinically and statistically significant decrease of ambulatory 24h and daytime blood pressure • Both doses of OM were able to lower nighttime ambulatory SBP

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and DBP statistically and clinically significantly compared to baseline and compared to AML. AML did not have an effect on nighttime ambulatory blood pressure

- All treatments led to a statistically and clinically significant decrease of UACR
- Only the two OM doses led to a clinically and statistically decrease of pulse wave velocity
- There were no clinically or statistically significant results with regard to the effects of OM in comparison to AML on markers of obesity, endothelial function, inflammation, diabetes, and arterial stiffness.
- All study treatments were safe and well tolerated which corresponds to the known good safety profiles of OM and AML.

Date of the Report: 10 March 2012