These Clinical Trial Results are provided for informational purposes only.

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2. SYNOPSIS

Name of Sponsor: Daiichi Sankyo Europe GmbH	Individual Study Table Referring to Part < < insert part #>> of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Olmesartan		
Name of Active Ingredient: Olmesartan medoxomil		

Title of Study: Randomised Olmesartan And Diabetes MicroAlbuminuria Prevention study (ROADMAP). Protocol number: SE-866/44. EudraCT number: 2004-000506-52

Investigators: Multi-centre study. Principal and Coordinating Investigator: [redacted], Hannover Medical School, Hannover, Germany.

Study Centres: 262 study centres in Austria, Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Spain, Ukraine, and United Kingdom.

Publication (reference): Haller H, et al. Preventing microalbuminuria in patients with diabetes: rationale and design of the Randomised Olmesartan And Diabetes MicroAalbuminuria Prevention (ROADMAP) study. J Hypertens 2006;24(2):403-8.

Study Period:	**Phase of Development**:
First patient in: 21 Oct 2004 Last patient out: 02 Jun 2009	Phase 3b

Objectives:

The full study objectives and endpoints are provided in study protocol and the statistical analysis plan. A summary of these objectives and endpoints is provided below.

Efficacy:

The primary confirmatory objective of this ROADMAP study was to compare the time to first occurrence of (adjudicated) microalbuminuria (using morning spot urine collections, assessed from baseline until the occurrence of microalbuminuria) in patients receiving olmesartan 40 mg (on a background of other anti-hypertensive agents) versus patients receiving placebo (on a background of other anti-hypertensive agents) during the double-blind treatment period. Microalbuminuria was defined as a urine albumin/creatinine ratio > 35 mg/g for women and > 25 mg/g for men. If the urine albumin/creatinine ratio during the study rose above this threshold the investigator had to confirm microalbuminuria by at least 1 further positive result out of 2 additional independent urine collections within 2 weeks.

Study hypothesis: the null hypothesis was that olmesartan medoxomil 40 mg was equal to placebo with regard to the time of occurrence of (adjudicated) microalbuminuria during the double-blind period.

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Secondary objectives were exploratory in nature and compared the 2 treatment groups with regard to time to event during the double-blind period of the following adjudicated secondary endpoints:

Cardiovascular (CV) events:

- CV Morbidity: acute coronary syndrome (ACS), congestive heart failure (CHF), silent myocardial infarction (MI), coronary revascularisation (percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass graft [CABG]), stroke, peripheral vascular disease (PVD), new-onset atrial fibrillation (AF), transient ischaemic attack (TIA)

- CV Mortality: Sudden cardiac death, fatal MI, fatal stroke, CHF death, death post PTCA or CABG, recent MI on autopsy

- Total mortality (CV mortality, death not CV related, death of unknown cause)

(NOTE: Combined endpoint A consisted of all CV morbidity and CV mortality events; combined endpoint B consisted of all combined endpoint A events without TIA and new-onset AF)

Renal function:

- End-stage renal disease

- Doubling serum creatinine

- Estimated glomerular filtration rate (eGFR) decrease

Retinopathy

Microvascular morbidity:

- Combination of retinopathy and microalbuminuria

All primary and secondary endpoints were adjudicated by an independent endpoint monitoring committee (EMC).

Safety and Tolerability:

Safety and tolerability were assessed in terms of treatment-emergent adverse events (TEAEs), vital signs (standing position), electrocardiogram (ECG), physical examination, and laboratory parameters (biochemistry, haematology, and urinalysis).

This synopsis focuses primarily on the results from the double-blind randomised period. However, a brief summary of the efficacy and safety results from the open-label and observation periods is also provided, with further details on these analyses provided in the main body of the report.

Methodology:

This phase 3b study was a randomised, placebo-controlled, double-blind, multi-national, multi-centre, primary prevention study with 2 parallel groups, conducted in 262 investigational sites across Europe.

After screening, eligible patients proceeded into the pre-randomisation period, which lasted for a

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maximum of 4 weeks. During this period the patients remained on their usual care treatment and the presence of microalbuminuria was excluded. Eligible patients were then randomised to receive either 40 mg olmesartan medoxomil once daily or matching placebo once daily. Blood pressure (BP) was tightly controlled during the course of the trial and physicians were instructed by the protocol to treat patient to BP goal (<130/80 mmHg) by allowing other antihypertensive medication(s) (except chronic use of angiotensin receptor blockers [ARBs] and angiotensin converting enzyme [ACE] inhibitors) in addition to the study medication, if necessary.

The study was planned to conclude when 326 adjudicated events of microalbuminuria had been reported. If a patient was diagnosed with microalbuminuria they stopped the double-blind treatment and proceeded into an open-label period (receiving 40 mg olmesartan medoxomil). Patients reporting MI, stroke or developing a creatinine clearance (CL_{CR}) < 30 mL/min stopped the double-blind period or the open-label period and entered into the observation period (without any study medication). Patients remained in the periods until the Final Examination/Premature Termination visit of the study (it was not possible to re-enter the double-blind treatment period or the open-label period).

Duration of Treatment:

The study was planned to be concluded when 326 adjudicated events of microalbuminuria were reported, or a maximum duration of 5 years, whichever occurred first. The study stopped after 326 adjudicated microalbuminuria events had occurred, resulting in 388 adjudicated events after study finalization, with a median follow-up duration of 3.2 years in the double-blind period.

Number of Patients:

Planned: 4400 randomised patients (2200 in each treatment group)

Screened: 5634 patients

Enrolled: 4512 patients

Randomised: 4449 patients (2233 olmesartan and 2216 placebo)

Randomised and treated: 4447 patients (2232 olmesartan and 2215 placebo)

Completed under double-blind treatment: 3011 patients (1534 olmesartan and 1477 placebo)

Completed under open-label treatment: 288 patients (132 olmesartan and 156 placebo)

Completed under observation period: 50 patients (21 olmesartan and 29 placebo)

Discontinued under double-blind treatment: 1438 patients (699 olmesartan and 739 placebo)

Discontinued under open-label treatment: 62 patients (32 olmesartan and 30 placebo)

Discontinued under observation period: 19 patients (12 olmesartan and 7 placebo)

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Diagnosis and Main Criteria for Inclusion:

Male or female Caucasian patients, aged 18 – 75 years (inclusive), with type 2 diabetes mellitus, defined by the American Diabetes Association (ADA) criteria (fasting blood glucose ≥ 126 mg/dL [7 mmol/L]), or receiving treatment for diabetes, who had at least 1 of the following cardiovascular risk factors:

- lipid disorder (defined as total cholesterol > 200 mg/dL [5.2 mmol/L] or receiving treatment for hyperlipidaemia)
- high density lipoprotein (HDL) cholesterol < 40 mg/dL (1.1 mmol/L)
- triglycerides > 150 mg/dL (1.7 mmol/L) and < 400 mg/dL (4.5 mmol/L)
- hypertension: systolic blood pressure (sBP) ≥ 130 mmHg and/or diastolic blood pressure (dBP) ≥ 80 mmHg or use of antihypertensive medication
- obesity (body mass index [BMI] ≥ 28 m^2/kg)
- waist circumference > 102 cm for men and > 88 cm for women
- smoking more than 5 cigarettes a day.

In addition, patients had to have:

- normoalbuminuria at screening of ≤ 35 mg albumin/g urine creatinine for women and ≤ 25 mg albumin/g urine creatinine for men (confirmed by 2 independent measurements within 2 weeks)
- haemoglobin A_{1c} glycohaemoglobin (HbA_{1c}) ≥ 6.5% for patients not receiving treatment for diabetes.

Investigational Product and Comparator Information:

Dosage Form: Olmesartan medoxomil 40 mg film-coated tablets once daily

Comparator: Olmesartan medoxomil matching placebo film-coated tablets once daily

Route of Administration: Oral

Batch numbers: Olmesartan 40 mg: Supply 1: [redacted]

Packaging Information: Tablets were packaged in blister packs, with 21 tablets per strip. Patients were supplied with boxes containing either 5 or 10 strips (ie, 105 or 210 tablets), depending on the visit.

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Criteria for Evaluation:

Efficacy:

Primary efficacy endpoint: time to the first occurrence of microalbuminuria (adjudicated by EMC) during the double-blind period, defined as albumin excretion in morning urine (collected as spot urine) of > 35 mg albumin/g urine creatinine for women and > 25 mg albumin/g urine creatinine for men, confirmed by at least 2 out of 3 independent measurements.

Secondary endpoints: time to the first occurrence of adjudicated events during the double-blind period, using all secondary efficacy endpoints as defined in the secondary objectives.

Other secondary quantitative endpoints: absolute change from baseline by visit in urine albumin/creatinine ratio, urine albumin, urine creatinine, eGFR, triglycerides, HbA_{1c}, mean sitting sBP and dBP, mean sitting pulse pressure, mean sitting heart rate. In addition for selected sites and restricted to patients who terminated/completed the study in the double-blind period, the change from screening to last assessment within the double-blind period for ambulatory blood pressure monitoring (ABPM) 24-hour mean, ABPM daytime mean and ABPM night-time mean for sBP and dBP were recorded.

Other important secondary qualitative endpoints: number of patients reaching BP goal (defined by mean sitting sBP/dBP < 130/80 mmHg), and number of patients showing BP response (defined as mean sitting sBP/dBP < 120/80 mmHg).

Safety:

Incidence, severity, seriousness, and action taken of TEAEs (based on Preferred Terms [PT] and primary System Organ Class [SOC] using MedDRA), vital signs (sBP, dBP and heart rate in the standing position, body weight and BMI), 12-lead ECG, and laboratory parameters (biochemistry, haematology, urinalysis).

Statistical Methods:

All target parameters were presented together with the appropriate descriptive statistics and graphical representations.

The Safety Set for the double-blind period (SAF-DB) consisted of all randomised patients with at least 1 intake of double-blind study medication. The Full Analysis Set for the double-blind period (FAS-DB) consisted of all randomised patients with at least 1intake of double-blind study medication. The restricted Full Analysis Set for the double-blind period (RFAS-DB) consisted of all patients from the FAS-DB excluding all patients having confirmed microalbuminuria at baseline (Visit 1) and patients without any evaluable follow-up evaluation of microalbuminuria during the double-blind period. The RFAS-DB was only used for the confirmatory analysis of the primary efficacy parameter, the exploratory analysis of the incidence rates of microalbuminuria and the exploratory analysis of the quantitative secondary efficacy parameters related to spot urine collection, but not for any analyses of secondary efficacy parameters except microvascular morbidity.

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In the confirmatory statistical analysis, the primary endpoint, ie, the time to the first occurrence of adjudicated microalbuminuria during the double-blind period, was compared between olmesartan and placebo via Wald chi-square test and a 95.1% 2-sided confidence interval (CI) derived for the hazard ratio (HR) of treatments from a Cox regression model, with log-transformed ($base_{10}$) baseline urine albumin/creatinine ratio as a covariate.

All secondary endpoints were analysed in an exploratory manner using appropriate methods of statistical hypothesis testing and interval estimates of treatment differences based on the nature of the parameter.

The effects of potential prognostic factors on the primary and selected secondary endpoints were investigated by including the respective factor as a covariate into the models used.

Demographics and other baseline characteristics and safety parameters were summarised and compared descriptively between groups. Summary statistics were tabulated to assess safety and tolerability in terms of TEAEs, laboratory tests, ECGs and vital signs.

Summary:

Study Population and Demographic Data:

In total, 5634 patients were screened and 4512 patients were enrolled into the study; 4449 patients were randomised. In the statistical analysis, 4447 randomised patients (olmesartan: 2232 patients, placebo: 2215 patients) were included in the SAF-DB and FAS-DB populations (2 patients did not take any study medication). A total of 4299 patients (olmesartan: 2160 patients, placebo: 2139 patients) were included in the RFAS-DB. The median follow-up time in the double-blind period was 3.2 years.

Overall, 1025 patients (olmesartan: 506 patients [22.7%], placebo: 519 patients [23.4%]) discontinued prematurely from the study during the double-blind period. The most frequent reasons for premature discontinuation (excluding patients withdrawn after reaching the efficacy endpoint of microalbuminuria) were withdrawal of consent (olmesartan: 319 patients [14.3%], placebo: 332 patients [15.0%]), adverse events (olmesartan: 85 patients [3.8%], placebo: 89 patients [4.0%]) and lost to follow-up (olmesartan: 51 patients [2.3%], placebo: 57 patients [2.6%]).

The treatment groups were well balanced with regard to demographics and other baseline characteristics. The mean duration of diabetes at screening was 6.1 years. At screening, more than 97% of the patients had 2 or more risk factors, and approximately 94% of patients had hypertension defined by a sBP/dBP $\geq$ 130/80 mmHg or use of antihypertensive medication. At baseline, the mean HbA_{1c} was 7.65% and the mean BP was 136.2/80.6 mmHg. The mean eGFR at baseline was 84.86 mL/min/1.73 m^2.

Primary Efficacy Results for the Double-Blind Period:

During the double-blind period, 178 (8.2%) patients in the olmesartan group and 210 (9.8%) patients in the placebo group developed microalbuminuria (adjudicated by the EMC). Based on the primary analysis set, ie, the RFAS-DB, and with regard to the primary endpoint of the time to onset of adjudicated microalbuminuria, a risk reduction of 23% in favour of olmesartan was observed (HR: 0.770; 95.1% CI: 0.630 to 0.941; confirmatory p-value: 0.0104).

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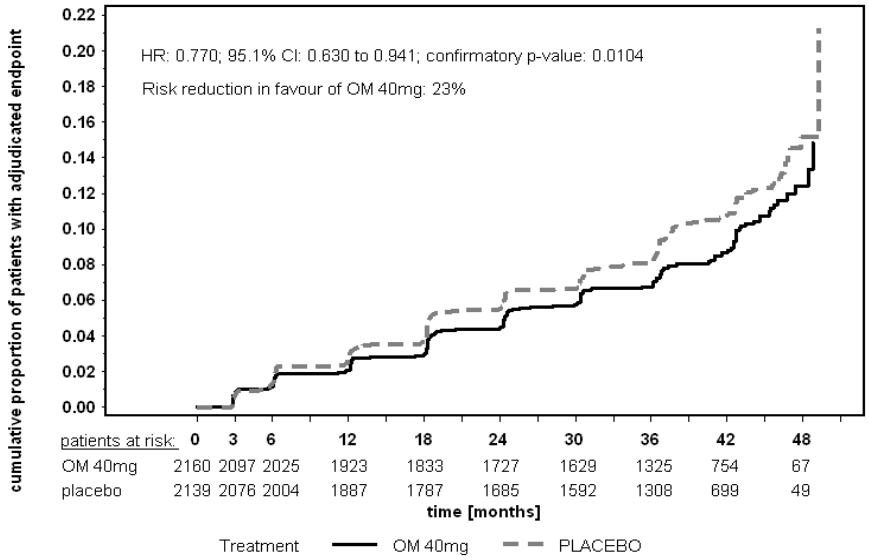

Kaplan-Meier Curve for the Cumulative Proportion of Patients with Adjudicated Primary Efficacy Endpoint of Microalbuminuria During the Double-Blind Period (RFAS-DB)

A 17% to 18% risk reduction in favour of olmesartan remained present after adjustment for BP differences using the pre-specified parameters area under the curve (AUC) sBP (HR: 0.834, 95% CI: 0.681 to 1.021, exploratory p-value=0.0789) and AUC dBP (HR: 0.823, 95% CI: 0.672 to 1.008, exploratory p-value: 0.0596) for the double-blind period.

Secondary Efficacy Parameters Related to BP for the Double-Blind Period:

The sBP/dBP control was very good during the double-blind period. At randomisation, approximately 30% of patients in both groups had a mean sBP < 130/80 mmHg. During the double-blind period, the percentage of patients reaching the target BP increased and was always larger in the olmesartan group compared to the placebo group. At Month 48, nearly 80% (330/422) of patients treated with olmesartan and approximately 71% (285/400) of patients treated with placebo achieved target BP (on a background of other anti-hypertensive agents). At the last assessment in the double-blind period, approximately 65% of the patients (olmesartan: 68.7%, placebo: 60.7%) had reached the target BP. It should be noted though that the total number of patients decreased as the study progressed, since patients dropped out due to a variety of reasons, including AEs such as hypertension.

Secondary Efficacy Endpoints for the Double-Blind Period:

A summary of the exploratory statistical results for all pre-specified adjudicated secondary efficacy endpoints in the FAS-DB is shown in the following table.

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	Incidence rates		Statistical analysis on time to event		
	Olmesartan (N=2232) n (%)	**Placebo (N=2215) n (%)**	**Hazard Ratio**	**2-sided 95% CI**	**Exploratory p-value[1]**
Combined endpoint A of CV events[2]	96 (4.3)	94 (4.2)	1.001	0.753 to 1.331	0.9935
Combined endpoint B of CV events[3]	78 (3.5)	74 (3.3)	1.034	0.752 to 1.421	0.8369
Combined endpoint of CV morbidity[4]	63 (2.8)	71 (3.2)	0.870	0.620 to 1.221	0.4202
Combined endpoint of other CV morbidity[5]	19 (0.9)	28 (1.3)	0.666	0.372 to 1.192	0.1707
Combined endpoint of CV and other CV morbidity[6]	81 (3.6)	91 (4.1)	0.872	0.646 to 1.176	0.3700
Combined endpoint of total mortality	26 (1.2)	15 (0.7)	1.704	0.903 to 3.217	0.1002
Combined endpoint of CV mortality[7]	15 (0.7)	3 (0.1)	4.940	1.430 to 17.061	0.0115
Combined endpoint of renal disease[8]	505 (22.6)	288 (13.0)	1.839	1.591 to 2.125	< 0.0001
- Worsening of renal function (Def. 1)	445 (19.9)	251 (11.3)	1.837	1.574 to 2.145	< 0.0001
- Serum creatinine increase (at least doubling from baseline)	23 (1.0)	23 (1.0)	0.979	0.549 to 1.745	0.9429
- eGFR reduction (>25% from baseline)	445 (19.9)	251 (11.3)	1.837	1.574 to 2.145	< 0.0001
- Worsening of renal function (Def. 2)	5 (0.2)	2 (0.1)	2.434	0.472 to 12.546	0.2878
- Worsening of renal function (Def. 3)	189 (8.5)	77 (3.5)	2.492	1.912 to 3.248	< 0.0001
- eGFR < 60 mL/min/1.73 m^2 at two consecutive visits (if eGFR ≥ 60 at baseline)	172 (7.7)	70 (3.2)	2.489	1.885 to 3.286	< 0.0001
- Worsening in CKD category, confirmed at the consecutive visit (if eGFR < 60 at baseline)	17 (0.8)	7 (0.3)	2.391	0.992 to 5.765	0.0522
-End-stage renal disease	0 (0.0)	0 (0.0)			
Retinopathy	10 (0.4)	12 (0.5)	0.821	0.355 to 1.901	0.6460
Combined endpoint of microvascular morbidity (based on RFAS-DB)[9]	186 (8.6)	221 (10.3)	0.819	0.674 to 0.996	0.0454

1 Exploratory statistical analysis related to time to occurrence of each endpoint within DB period and based on a Cox proportional hazard model with treatment as fixed effect.
2 Endpoint A events include sudden cardiac death, death due to fatal MI, evidence of recent MI on autopsy, death due to CHF, death during or post PTCA or CBAG, death due to fatal stroke, ACS, CHF requiring hospital management, silent MI, coronary revascularisation, non-fatal stroke, PVD requiring hospital management, new-onset AF, TIA
3 Endpoint B events included all of the above, without new-onset AF and TIA
4 Combined endpoint of CV morbidity includes ACS, CHF requiring hospital management, silent MI, coronary revascularisation, non-fatal stroke, PVD requiring hospital management
5 Combined endpoint of other CV morbidity includes only new-onset AF and TIA
6 Combined endpoint of CV and other CV morbidity (ie, all CV morbidity) include ACS, CHF requiring hospital management, silent MI, coronary revascularisation, non-fatal stroke, PVD requiring hospital management; new-onset AF and TIA
7 Combined endpoint of CV mortality include sudden cardiac death, death due to fatal MI, evidence of recent MI on autopsy, death due to CHF, death during or post PTCA or CBAG, death due to fatal stroke
8 Category expanded based on pre-defined criteria in the statistical analysis plan of a significant treatment difference and a difference in the number of observed events of ≥ 23 events
9 Combined endpoint of microvascular morbidity include retinopathy and microalbuminuria
Definition 1: serum creatinine increase (at least doubling from baseline) and/or eGFR reduction (> 25% from baseline)
Definition 2: serum creatinine increase (at least doubling from baseline), confirmed by a second measurement after at least 4 weeks and/or serum creatinine increase (at least doubling from baseline) leading to hospitalisation
Definition 3: eGFR < 60 mL/min/1.73 m^2 at 2 consecutive visits (for patients with eGFR ≥ 60 mL/min/1.73 m^2 at baseline and/or worsening in chronic kidney disease (CKD) category, confirmed at the consecutive visit (for patients with eGFR < 60 mL/min/1.73m^2 at baseline).

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Secondary Cardiovascular Endpoints for the Double-Blind Period:

The number of patients reaching the combined endpoint A of cardiovascular events was low and similar in both groups: 96 patients (4.3%) with olmesartan and 94 patients (4.2%) with placebo. Cardiovascular morbidity events including TIA and new-onset AF occurred numerically less often in the olmesartan group compared to the placebo group (81 [3.6%] vs. 91 [4.1%]).

Total mortality occurred in 26 patients (1.2%) in the olmesartan group and 15 patients (0.7 %) in the placebo group, with no statistically significant difference between the two groups (HR: 1.704; 95% CI: 0.903 to 3.217; exploratory p-value=0.1002). Cardiovascular mortality was higher in the olmesartan group (15 events [0.7%] vs. 3 events [0.1%]; HR: 4.940; 95% CI: 1.430 to 17.061; exploratory p-value: 0.0115). This difference in fatal endpoints was due to a higher number of patients with fatal MI (5 vs. 0) and sudden cardiac death (7 vs. 1). In none of these cases did the investigator attribute the mortality to the study medication.

Secondary Renal Efficacy Endpoints for the Double-Blind Period:

The combined endpoint of renal disease (consisting of events relating to eGFR decline, doubling of serum creatinine and end-stage renal disease) showed a statistical significant difference between the 2 groups in favour of placebo. However, the majority of the reported renal events were derived from an eGFR decline >25%. The incidence of severe renal endpoints (doubling of serum creatinine and end-stage renal disease) showed no difference between the groups. Twenty three patients each in the olmesartan and placebo group experienced a doubling of serum creatinine compared to baseline. No patient in either group developed end-stage renal disease.

The mean (±SD) eGFR declined in the olmesartan group from 85.0 (±17.0) at baseline to 80.1 (±18.5) mL/min/1.73 m^2 at the last assessment within the double-blind period, and in the placebo group from 84.7 (±17.3) to 83.7 (±18.4) mL/min/1.73 m^2 (exploratory p-value for absolute change from baseline to last visit < 0.0001). At Month 6, the LS mean difference (ANCOVA) for eGFR was 2.8 mL/min/1.73 m^2 in favour of placebo. Mean eGFR was still within the physiological range (ie, >80 mL/min/1.73 m^2) at last assessment in both treatment groups.

Other Secondary Efficacy Endpoints for the Double-Blind Period:

The number of patients with retinopathy was comparable between groups, with 10 patients (0.4%) in the olmesartan group and 12 patients (0.5%) in the placebo group. The combined endpoint for microvascular disease (microalbuminuria and retinopathy) was less common in patients treated with olmesartan compared to placebo (186 [8.6%] vs. 221 [10.3%] patients; HR: 0.819; 95% CI: 0.674 to 0.996, p-value: 0.0454).

Efficacy Results for Open-Label and Observation Periods:

In the open-label period, reversion to sustained normoalbuminuria (adjudicated by the EMC) was achieved by 41.0% of patients previously treated with olmesartan and by 43.6% of patients previously treated with placebo.

During the observation period, 4 patients (12.1%) developed microalbuminuria (adjudicated by the EMC) in the prior olmesartan group compared to 2 patients (5.6%) in the prior placebo group.

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During the open-label period, 8 patients (4.9%) in the prior olmesartan group and 10 patients (5.4%) in the prior placebo group experienced secondary combined endpoint A. During the observation period, 3 patients (9.1%) in the prior olmesartan group and 6 patients (16.7%) in the prior placebo group did so.

During the open-label period, no patients in the prior olmesartan group and 1 patient (0.5%) in the prior placebo group experienced cardiovascular mortality. There was no cardiovascular mortality during the observation period.

Since in both the open-label and observation periods most of the secondary efficacy events only occurred in few patients, no conclusions are drawn from this data.

Safety Results for the Double-Blind Period:

An overview of the safety results in the double-blind period (SAF-DB/FAS-DB) is shown in the following table.

Brief summary of AEs (Patients with TEAEs)		Olmesartan N = 2232 n (%)	Placebo N = 2215 n (%)	Total N = 4447 n (%)
At least 1 TEAE		1724 (77.2)	1666 (75.2)	3390 (76.2)
At least 1 serious TEAE		335 (15.0)	337 (15.2)	672 (15.1)
At least 1 TEAE by highest severity grade	(mild)	925 (41.4)	910 (41.1)	1835 (41.3)
	(moderate)	628 (28.1)	602 (27.2)	1230 (27.7)
	(severe)	171 (7.7)	153 (6.9)	324 (7.3)
At least 1 laboratory TEAE		995 (44.6)	878 (39.6)	1873 (42.1)
At least 1 TEAE leading to discontinuation from study		83 (3.7)	88 (4.0)	171 (3.8)
At least 1 TEAE leading to discontinuation of study medication (defined by action taken on study drug=discontinued on AE CRF)		134 (6.0)	139 (6.3)	273 (6.1)
Any TEAE leading to death		26 (1.2)	15 (0.7)	41 (0.9)
At least 1 drug-related TEAE		255 (11.4)	166 (7.5)	421 (9.5)
At least 1 drug-related serious TEAE		4 (0.2)	1 (0.0)	5 (0.1)
At least 1 drug-related TEAE by highest severity grade	(mild)	175 (7.8)	114 (5.1)	289 (6.5)
	(moderate)	69 (3.1)	46 (2.1)	115 (2.6)
	(severe)	10 (0.4)	6 (0.3)	16 (0.4)
At least 1 drug-related laboratory TEAE		89 (4.0)	58 (2.6)	147 (3.3)
At least 1 drug-related TEAE leading to discontinuation from study		35 (1.6)	30 (1.4)	65 (1.5)
At least 1 drug-related TEAE leading to discontinuation of study medication		37 (1.7)	31 (1.4)	68 (1.5)
Any drug-related TEAE leading to death		0 (0.0)	0 (0.0)	0 (0.0)

Solicited primary and secondary EMC-adjudicated efficacy endpoints were also reported as TEAEs by the investigators. For this synopsis, the decision was made to discuss TEAEs related to adjudicated events in the efficacy section (eg, microalbuminuria, GFR decreased, renal impairment) and to focus here on the TEAEs spontaneously reported by the investigator. All TEAEs, whether adjudicated or not, will be reported and discussed in the main body of the report.

The most common spontaneously reported TEAEs include headache (olmesartan: 100 [4.5%] patients, placebo: 153 [6.9%]), bronchitis (olmesartan: 102 [4.6%] patients, placebo 104 [4.7%] patients), and nasopharyngitis (olmesartan: 112 [5.0%] patients, placebo 94 [4.2%] patients).

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Few of the TEAEs were considered by the investigators to be drug-related. The most common drug-related TEAEs (including both spontaneously reported and TEAEs related to efficacy endpoints) were renal impairment (olmesartan: 34 [1.5%] patients, placebo: 13 [0.6%] patients), hypotension (olmesartan: 41 [1.8%] patients, placebo: 4 [0.2%] patients), GFR decreased (olmesartan: 29 [1.3%] patients, placebo: 13 [0.6%] patients), and dizziness (olmesartan: 29 [1.3%] patients, placebo: 10 [0.5%] patients).

A total of 1.5% patients had study medication discontinued during the double-blind period due to at least 1 drug-related TEAE (olmesartan: 37 [1.7%] patients, placebo: 31 [1.4%] patients). The most common drug-related TEAE that led to discontinuation was hypotension (olmesartan: 11 [0.5%] patients, placebo: 1 [0.0%] patient), followed by headache (olmesartan: 3 [0.1%] patients, placebo: 5 [0.2%] patients), and abdominal pain, dizziness and vertigo (olmesartan: 3 [0.1%] patients, placebo: 1 [0.0%] patient).

No clinically meaningful changes from baseline or differences between the groups in mean haematology, biochemistry and urinalysis variables at any time during the double-blind period of the study were observed. A small increase in mean creatinine values between baseline and last visit of the double-blind period in the olmesartan group (4.48 μmol/L) was observed, but relatively little change was seen in the placebo group (0.51 μmol/L). This is in line with the known safety profile of olmesartan. Clinically relevant shifts (as judged by investigators) in biochemistry variables (hepatic enzymes, blood glucose, and blood lipids) were similar in both groups and of no concern regarding the patient population. There were no differences of note in vital signs or ECGs between the 2 treatment groups.

Safety Results for the Open-Label and Observation Periods:

During the open-label period, the proportion of patients with at least 1 TEAE was similar in the prior olmesartan and prior placebo groups (105 [64.0%] versus 122 [65.6%] patients).

During the observation period, the proportion of patients with at least 1 AE was similar in the prior olmesartan and prior placebo groups (17 [51.5%] versus 17 [47.2%] patients).

The frequency of all TEAEs reported during the open-label period, as well as all AEs reported during the observation period, was similar among both groups.

Conclusions:

The primary objective of the ROADMAP study was met, ie, it was demonstrated in the confirmatory analysis that olmesartan 40 mg is able to significantly delay the time to onset of microalbuminuria compared with placebo. The primary objective was reached under very good blood pressure control during the double-blind period in both treatment groups, with more pronounced blood pressure control in the olmesartan 40 mg group.

Overall, the number of adjudicated cardiovascular efficacy endpoints was very low in this study. The interpretation of the cardiovascular event findings is challenging as indicated by the numerical trend in favour of olmesartan 40 mg in cardiovascular morbidity and an opposite finding in cardiovascular mortality. Based on these inconsistent findings and the very low number of events, it was concluded that no new safety concern for olmesartan emerged.

The rate of severe renal events (doubling of serum creatinine or end-stage renal failure) was very low in the study and identical between the 2 treatment groups. There was a more pronounced decrease in eGFR

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in the olmesartan group than in the placebo group. Mean eGFR was still within the physiological range (ie, > 80 mL/min/1.73 m^2) at last assessment in both treatment groups. The inhibition of the RAS system by olmesartan and the subsequent reversal of hyperfiltration might be the main contributing factors for this eGFR-lowering effect of olmesartan.

Comparison of the investigator-reported TEAEs assessed by intensity, severity, causality, and seriousness did not show any new safety concern for olmesartan-treated patients, and safety findings are in line with the known safety profile for olmesartan.

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